EXHIBIT 9

Websters Encyclopedic Unabridged Dictionary of the English

The dictionary entries are based on the First Edition of The Random House Dictionary of the English Language

PORTLAND HOUSE • NEW YORK

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homo-

Greek, where it meant "same" (homology); on this model, used in the formation of compound words (homomorphic). Also, esp. before a rowel, home. [< Gk, comb. form of homos one and the same; akin to Skt sama; see SAME]

Also, sp. before a vowel, hom.— [< Gk, comb. form of homos one and the same; akin to Skt sama; see same] homos one and the same; akin to Skt sama; see same] homos one and the same point. homo-p, n. isobront. [Homo-+-bront, as in isobront] homo-centric floyms sen'trik, hom/-), adj. 1. having a common center; concentric. 2. diverging from or converging to the same point: homo-centric rays. Also, ho/mo-cen'trical. [Homo-+ central]. homo-en'trical. ly, adv. homo-cen'trical. ho/mo sur'ks]. hom/-), adj. Ichthyol. 1. having an equally divided tail or caudal fin. the spinal column ending at or near the middle of the base of the tail. 2. noting such a tailor caudal fin. Cf. heterocercal. [Homo-tail-ty (hō/ma sarks]/tis, hom/-), ho-mo-cen-cal-ti-ty (hō/ma sarks]/tis, hom/-), ho-mo-cen-cal-ti-ty (hō/ma sarks]/tis, hom/-), ho-mo-chromatic. [Cf. homo-chromatic. [Homo-+ Chromatic. [Homo-+ Chromatic. [Homo-+ Chromatic. [Homo-+ Chromatic. [Homo-+ Chromatic.]/tis hom/-), adj. homo-chromatic. [Cf. homo-chromatic. [Ko/ma krō/mas, hom/-), adj. homo-chromo-tromous (hō/ma krō/mas, hom/-), adj. homo-chromo-tromous (hō/ma krō/mas, hom/-), adj. homo-chromous (hō/ma krō/mas, hom/-), adj. homo-chromo-tromous (hōma krō/mas, hom/-), adj. homo-chromous (hōm

my (hō/me krō/mē, hom/ə-), n.
ho-moch-ro-nous (hō mok/re nes, ho-), adj. (of a genetic character) occurring at the same age or period in the offspring as in the parent. [< Gk homochrones of the same time. See HoMO-, CHRON-, -OUS]
ho-mo-cy-chic (hō/me si/klik, -sik/ilk, hom/ə-), adj.
Chem. of or noting a cyclic compound having atoms of only one element, usually carbon, in the ring. [HOMO-+ CYCLIC]

+ cyclic]
ho-mo-dyne (hō/mo din/, hom/o-), adj. Radio. of or pertaining to reception by a device that generates a varying voltage of the same or nearly the same frequency as the incoming carrier wave and combines it with the incoming signal for detection. [HOMO-+ DYNE]

incoming signal for detection. [HOMO-+ DYNE]
homoeo-, var. of homoeo-: homosopathy.
ho-moe-o-morph (hō/mē ə mōrt/), n. homeomorph.
ho-moe-o-mor-phism (hō/mē ə mōrt/iz əm), n. homeomorphism. —ho/moe-o-mor/phic, ho/moe-o-mor/phous, adj.

phous, adj.

ho-moe-op-a-thist (hō/mē op/e thist), n. homeopathist. Also, ho-moe-o-path (hō/mē ə path/).

ho-moe-op-a-thy (ho/mē op/e thē), n. homeopathy.

—ho-moe-op-ath-ic (hō/mē ə path/ik), adj.

—ho-moe-roti-cism (hō/mē i rot/isiz/əm), n. Psychicism to-op-ath-ic ho-sevually aroused by a member of

atry. a tendency to be sexually aroused by a member of the same sex. Also, he mo-er-o-tism (hō/mō er/ə tiz/əm). [HOMO- + BROTICISM] —ho-mo-e-rot-ic (hō/mō i rot/-

h(), aa; ho.mo-fer-ment a tive (hō/mō fer men/te tiv, hom/-ō-), adj. Biochem. producing a fermentation that results in one end product. Cf. heterofermentative. [HOMO-+ FERMENTATIVE]

in one end product. (c). Neteroterimentarive: [no.mog.a.mous (hō mog/a məs), adj. Bot. 1. having flowers or florets which do not differ sexually (opposed to heterogamous). 2. having the stamens and pistils maturing simultaneously (opposed to dichogamous). [< Gk homogamos married to sisters, or to the same woman. See homo-, -Gamous] homog-a.my (hō mog/a mē), n. 1. Bot. state of being homogamous. 2. interbreeding of individuals of like characteristics. [homo-+-Gamy] homo-ge-ne-1-fy (hō/mə ja nē/i tē, hom/ə-), n. composition from like parts, elements, or characteristics; state or quality of being homogeneous. Also, ho-mo-ge-ne-ous-ness (hō/mə jē/nē əs nis. -jēn/yəs, hom/ə-), [< ML homogenetis. equiv. to homogeneous romogeneous homogeneous (hō/mə jē/nē əs nis.)

[< ML homogeneils. equiv. to homogene(us) homogeneous + itis-irr] lome js/ns s., -jsn/ys, hom/s-), adj. 1. composed of parts all of the same kind; not heterogeneous: a homogeneous population. 2. of the same kind on nature; essentially alike: homogeneous parts. 3. Math. a. having a common property throughout: a homogeneous soid figure. b. having all terms of the same degree: a homogeneous equation. e. remaining unchanged when each variable is replaced by the same specified number times the variable: a homogeneous function. d. (of an equation) formed by equating a homogeneous function to zero. e. relating to a function of several variables which can be written as a new function of the variables which can be written as a new function of the derivatives can be written as a linear combination of letrus containing as the variable the dependent variable of the derivative divided by the independent variable. [< ML homogeneus, equiv. to homogene-(s. of Gk homogeneous-ly, adv. homoge/neous-ly, adv. homoge/neous-ly, adv. homoge/neous coor/dinates, Geom. a coordinate system used in projective geometry in which a point in the plane is represented by three numbers, the ratio of the first to the third being its ordinate and the ratio of the second to the third being its ordinate and the ratio of the production in which the offerive resemble the new long energy in which a point in the plane is represented by three numbers, the ratio of the first to the third being its ordinate and the ratio of the first to the third being its ordinate and the ratio of the production in which the offerive resemble the negretal parts.

ho-mo-gen-e-sis (hō/mə jen/i sis, hom/a-), n. Biol. reproduction in which the offspring resemble the parent and undergo the same cycle of development. [HOMO-+ GENESIS]

+ GENERIA + GENERIC - Holmogenetical - Holmogenetical + GENERIC - Holmogenetical - Holmogenetica

+ GENETIC] —ho/mo-ge-net/i-cal-ly, adv.
ho-mog-e-nize (ha mo//a niz/, hō), v.t., -nized, -nizing. 1. to form by blending unlike elements; make
homogeneous; emulsify. 2. to break up the fat globules
in (milk or cream) in order to distribute them equally
throughout. [HOMOGEN(SOUS) + -1zz] —ho-mog/e-nizzz/tion, n. —ho-mog/e-niz/er, n.

man; OL hemō the earthly one; akin to L humus earth, no-mog-e-nous (he moj/e nes, hō-), adj. 1. Biol. corsoil, hūmānus нимам, OE guma man, Gk chamat on the responding in structure because of a common origin, homo-nym (hom/e nim), n. 1, a word like anot ground] homo-, an element appearing in loan words from homo-, an element "same" (homology); on this model, losd the formation of compound words (homomorphic). Also, esp. before a vouel, hom-. [< Gk, comb. form of homos one and the same; akin to Skt same; see same] homos one and the same; akin to Skt same; see same] homos one and the same; akin to Skt same; see same] homobront (hō/me bront/, hom/e-), n. isobront.

HO.MOG. CALD! No. Mod. ACD! no. Mod. No. Mod. Correspondence in form or structure, owing to a common origin. [< Gk homogeneia community of origin. See HOMO., -GENY]

[< Gk homogeneta community of origin. See Homo-gany]
ho-mog-o-nous (he mog'e nes, hō-), adj. Bot. pertaining to monoclinous flowers which do not differ in the relative length of stamens and pistils (opposed to heterogenous). [HOMO-+-gonous < Gk -gonos generating; see -gony] -ho-mog'e-nous-ly, adv.
ho-mog-o-ny (he mog'e nē, hō-), n. Bot. state of being homogonous. [HOMO-+-gony]
ho-mog-graft (hō/me graft/, -grāft/, hom/e-), n. Surg. a tissue or organ obtained from one member of a species and transplanted by grating to another member of the same species. Also called isograft, isoplastic graft. Cf. autograft, heterograft. [HOMO-+ GRAFT]
hom-o-graph (hom/e graf/, -grāf/), n. a word of the same written form as another but of different origin and meaning, as homer! "home run." and home? "unit of measure." [HOMO-+ -GRAFT]—-hom-o-graphic (hom/e graf/ik), adj.
ho-moi-o-therm (hō moi/e therm/), n. Zool. a homoi-othermal animal. Also, homeothermal.
ho-moi-o-thermal (hō moi/e ther/me), adj. Zool.

othermal animal. Also, homeotherm, homotherm. [back formation from Homotothermal.]

ho-moi-other mal (hō moi/e thūr/mel), adj. Zool. having a body temperature that is relatively constant and mostly independent of the temperature of the environment; warm-blooded (opposed to poikitothermal). Also, ho-moi/other/moi homeothermal. [HOMOIO- + THERMAL]—ho/moi-other/my, ho/moi-other/mism, n.

Ho-moi-ou-si-san (hō/moi ōō/sē an, -ou/-), n. I. one of a 4th-century A.D. church party which maintained that the essence of the Son is similar to, but not the same as, that of the Father. —adj. 2. relating to the Homoiousians or their belief. (< Lōk homoious(s) of like substance (homoi- HOMOIO) - + ous(a) substance, essence + -os adj. suffix) +-AN]—Ho/moiou/si-anism, n.

ho-mo-leci-thal (hō/males/athel), adj. Embryol.
having a fairly uniform distribution of yok, as certain eggs or ova having relatively little yolk. [HOMO- + LECITHAL]
ho-mol-ogate (ha mol/agāt/, hō-), v.i., -gat-ed, -gat-

ming carrier wave and support of the control of the

De nomologous; correspond. (HOMOLOG(OUS) + -IZE)
—ho-moll-O-gous (he moll-2 gas, hō-), adj. 1. having the
same or a similar relation; corresponding, as in relative
position, structure, etc. 2. Biol. corresponding in
structure and in origin, but not necessarily in function:
The wing of a bird and the foreleg of a horse are homologous. 3. Chem. of the same chemical type, but differing
by a fixed increment in certain constituents. 4. Immunol., Med. pertaining to the relation between bacteria
and the immune serum prepared from them. [< ML
homologus < Gk homologos agreeing, equiv. to homonomo-+logos proportional, equiv. to hg-(s. of légos
proportion; see Logos) +-os-ous]
homologous chro/mosomes, Biol, pairs of similar chromosomes, one of maternal, the other of paternal
origin, which carry the Mendelian pairs of alleles or
genes.

genes.

ho-mol-o-graph-ic (hō mol/ə graf/ik), adj. representing parts with like proportions. Also, homalographic.

[Var. of Homalographic projection, Cartog. an equalarea projection in which the proportion between regions
of unequal area is correctly shown. Also called Mollweide projection.

weide projection.

hom-o-logue (hom/e lôg', -log'), n. 1. something homologous. 2. Biol. a homologous organ or part. 3. Chem. any member of a homologous series of organic compounds: Ethene is a homologue of the altane series. [< Gk homolog(on), neut. of homologos noncologous] ho-mo-lo-gu-me-na (hō'mō lo gōō'mə na, -gyōō'-), n. (construed as sing.) the books in the New Testament generally held as authoritative and canonical by the early church. Also, ho'mo-lo-gou'me-na. Cf. antilegomena. [< Gk (neut pl.), deriv. of homologen to agree to, allow; see homologous].

ho-moll-ogy (ha mol/a jē. hō-), n. pl. -gies. 1. state of

mens. 1 < Na (Intuty):1, tenth of homologues to agree to, allow; see HOMOLOGOUS]

ho-mol-o-gy (he mol/a 18, hō-), n., pl. -gies. 1. state of being homologous; homologous relation or correspondence. 2. Biol. a. a fundamental similarity of two segments of one animal based on a common developmental origin. 3. Chem. the similarity of organic compounds of a series in which each member differs from its adjacent compounds by a fixed increment, as by CH₂. 4. Math. a classification of figures according to certain geometric properties. [< Gk homologi(a) agreement, equiv. to homologo(s) Homologous +-id-x²]

homol/o-sine projection (he mol/a sin, -sin/, hō-, Cartog, an equal-area projection of the world, distorting ocean areas in order to minimize the distortion of the continents. [irreg. HOMOLO (GRAPHIC) + SINE¹]

homon-point (hō/me môr/lik, hom'ə-), adi, Math.

ho-mo-mor-phic (ho/me mor/fik, hom/e-), adj. Math. pertaining to two sets that are related by a homomorphism. [HOMO- + -MORPHIC]

homothetic

hom-o-nid (hom's nid), n. Anthropol. hominid.
hom-o-nym (hom's nim), n. 1, a word like another in sound and spelling but different in meaning, as chase, to pursue, and chase, to ornament metal. 2. a homophone. 3. a homograph. 4. a namesake. 5. Blol. a name given to a species or genus which has been used at an earlier date for a different species or genus and which is therefore rejected, [LiLhomönym(um) Cek homonymos nown-nym'i-ty, n. homony-mous (he mon's mes, hō-), adj. of the nature of homonyms; having the same name. [Lhomonymus Cek homonymos nown+ns, homon'y-mous (he mon's mes hō-). adj. of the nature of homonyms; having the same name, equiv. to hom(o)- homo-+ homon'd) name, -0xxx+-os-ous |
-homon'y-mous-iy, ads.

—no-mon'y-mous-ny, aan.
homon'y-mous construction, Gram. a construction that consists of the same morphemes in the same order as those of another construction, as Flying planes and be dangerous, in which planes in one construction is the object of flying, and in another the subject of can; a terminal string of formatives having two or more structural descriptions.

state. [< LL homonymia < Gk, equiv. to homonymous Homonymous + ia r³]

HOMONYMOUS + id - r¹]

Ho-mo-ou-si-an (hō/mō oō/sē ən, -ou/-, hom/ō-),

Eccles. —n. 1. one of a 4th century A.D. church party
which maintained that the essence or substance of the
Father and the Son is the same. (opposed to Heterorusian). —adj. 2. of or pertaining to the Homoousians or
their doctrine. Also, Ho/mo-du-sian. [< LGk homoousi(os) of the same substance (Gk hom(o)- Homo-yousi(a) substance, essence + -os adj. suffix) + -an]
—Ho/mo-ou/si-an-ism, n.

homo-ou/si-an-ism, n. Ho·mo·ou·si·an

He'mo-ou'si-ani-ism, n.
hom-o-pause (hom's pāz', hō'ms-), n. Meteorot.
Rars. the boundary or transition layer between the homosphere and the heterosphere. [EOMO-+ PAUSE] hom-o-phone (hom's fōn', hō'ms-), n. 1. Phonet, a word pronounced the same as, but differing in meaning from another, whether spelled the same way or not, as heir and air. 2. a written element that represents the same spoken unit as another, as ks, a homophone of x in English. [back formation from Homophone of x in

the same sound. 2. Music. having one part or melody predominating (opposed to polyphonic). [< Gk homo-phōn(a) (see homo-phonous) + -ic] —hom/o-phon/i-cal-ly, adv.

—no-mo-plastic (no/me) pass'ak, nom'e-), at, at, ho-mo-po-lar (no/me) po'ler, hom'e-), atj. Chem. of uniform polarity; not separated or changed into ions; not polar in activity. Homo-+ Polari —ho-mo-po-lar-i-ty (no'me) polarite, hom'e-), n.

Ho-mop-ter-a (no mop/ter-e), n. the order comprising the homopterous insects. [< NL (neut. pl.); see HOMOPTEROUS]

HOMOPTEROUS]
ho-mop-ter-ous (he mop/ter as, hō-), adj. belonging or pertaining to the Homoptera, an order of insects closely related to the hemipterous insects (in some classifications a suborder of Hemiptera) but having membranous forewings and hind wings, comprising the aphida, cicadas, etc. [< Gk homopteros. See HOMO-, -FTEROUS]

ous forewings and hind wings, comprising the aphids, cicadas, etc. [< dik hombjetors. See HoNo.— rpragous] ho-mor-gan-ic (hō/mōr gan/ik, hom/ōr-), adj. Phonet. (of two or more speech sounds) articulated by using the same speech organ or organs, as p, b, and m, which are homorganic with respect to being labilation to the trespect to being velar. (Cf. homotypical (def. 1). [HOMO 58.p1-ens (hō/mō sā/pē enz), 1. (italics) modern man, the single surviving species of the genus Homo and of the primate family Hominidae, to which it belongs. 2. mankind. [< L: man, the wise]
ho-mo-sex-u-sl (hō/mɔ sek/shōō əl, -mō-), adj. 1. of, pertaining to, or noting the same sex. —n. 3. a homosexual person. [HOMO—+ SEXUAL]
ho-mo-sex-u-sl-i-ty (hō/mɔ sek/shōō əl/i tā, -mō-), n. sexual desire or behavior directed toward a person or persons of one's own sex. [HOMO—+ SEXUALITY]
ho-mo-sphere (hō/mɔ sēk/shōō əl/i tā, -mō-), n. sexual desire or behavior directed toward a person or persons of one's own sex. [HOMO—+ SEXUALITY]
ho-mo-sphere (hō/mɔ sēk/shōō al/i tā, -mō-), n. which there are no gross changes in atmospheric composition. Cf. heterosphere. [HOMO—+ SPEKER]
ho-mos-po-rous (hə mos/pər əs, hō/mɔ spō/əs, -spōf/-), adj. Bol. having spores of one kind only. (ho-mos-po-ry (hə mos/pər əs, hō/n, spōf/əs, -spōf-), n. the production of a single kind of spore, neither microspore nor meas-

HOMO-+ SPORE + OUS]

ho-mos-po-ry (he mos/pers, hō-), n. the production of a single kind of spore, neither microspore nor megaspore, [HOMO-+ spore, neither microspore nor megaspore, [HOMO-+ spore, +r²]
ho-mo-styled (hō/mō stild/), adj. (of a plant) having styles of the same form or length in all flowers, Also, ho/mo-sty/lous, ho/mo-sty/lic, [HOMO-+ STYLED]—ho/mo-sty/lsm, ho/mo-sty/lsn, ho-mo-sty/lsn, ho/mo-sty/lsn, ho/mo-stx/lsn, ho/mo-s

al·ly, adt.

ho·mo·thal·lic (hō/me thal/ik, hom/e-), adj. Bot. 1.
having all mycelia alike, the opposite sexual functions
being performed by different cells of a single mycelium.

Of. heterothallic (def. 1). 2. monoecious. [HoMo-+
THALL (Us) + -tc] -ho/mo·thal/lism, n.
ho·mo·therm (hō/mɔ thlmm, hom/e-), n. homoiotherm. -ho/mo·ther/my, ho/mo·ther/mism, n.
ho·mo-ther-mal. (hō/mɔ thlmm, hom/e-), adj.
homoiothermal. Also, ho/mo·ther/mic, ho/mo·ther/mous.
ho·mo-thet-ic (hō/mo·ther/li).

homogenettic (hō/maja net/ik, hom/a-), ads. But.

1. pertaining to or characterized by homogenests 2.

1. pertaining to or characterized by homogenests 2.

1. pertaining to or characterized by homogenests 2.

1. homogenous (det. 1). Also, ho/mogenet/l-cal. [Homogenests 2.

1. homogenous (det. 1). Also, ho/mogenet/l-cal. [Homogenests 2.

1. homogenet/l-cal. [Homogenests 2.

1. homogenests 2.

1. homogenests 2.

1. homogenet/l-cal. [Homogenests 2.

1. homogenests 2.

2. homogenests 2.

2. homogenests 2.

3. homogenests 4.

3. 2ool. resemblance homochterm (ho/mother/mism. n.

4. homother/mism. homochterm (ho/mother/mism. n.

4. homother/mot

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in isolation. In I valked out when the belt rang, I led out is the main clause. Cf. dependent (def. 12). 5. Naul. a. of or pertaining to mainsail. [ME; see Main!, sheet!] sheet!] mainsail. [ME; see Main!, sheet!] sheat!] mainsail. [ME; see Main!, sheet!] sheat!] she

be North Pole: about 30 miles in diameter.

in bod/y, Naut. the hull, as distinguished from
he rest of a vessel.

in' brace', Naul. a brace leading to a main yard. in' brace', an opportunity offering the greatest in: Being ambilious, he always had an eye for the main

hance.

Tain' clause', Gram. a clause that can stand alone
is sentence, containing a subject, a predicate of
finite verb, and sometimes a direct object, as I was
fire in the sentence I was there when he arrived.
if: subordinate clause.

Tain' course', Naut. a square mainsall.

Tain' deck', I. Naut. the uppermost weatherproof
cieck, running the full length of a vessel. 2. (on a
fireat Lakes ore boat) a
partial deck at the level
of the tops of the side
sanks.

main-de-fer (man/a-fer/), n. Armor. manifer. main/ diag/onal, diag'onal, under diag-

main/ diag/onal, Math. See under diagbnal (def. 9).
main/ drag/, Slang.
the main street of a city
or town; main stem:
Broadway is New York's

QUEBEC Maine Bangor) main drag.

Maine (mkn), n. 1. a State in the NE United States, on the Atlantic coast. 969.265 (1960); Say. 115 a. (arrange former province in NW France. Cap.: Le Mans. S. ((talics) a U.S. battle-ship blown up in the charbor of Havana, Cuba, on February 15, 1898.

Maine-et-Loire (me/nā lwar/), n. a department shin W France. 556.272 (1962); 2787 sq. mi. Cap.: Angers.

Main-er (mā/nər), n. a native or inhabitant of the

Main-er (ma/nər), n. a native or inhabitant of the State of Maine.

State of Maine.

State of Maine.

Main-frame (mān/trām/), n. Computer Technol. a Marge high-speed computer with greater storage capacity ithan a minicomputer, often serving as the central unit in a system of smaller computers. [Main' + FRAME]

main gauche (man gōsh/), a dager of the 16th land 17th centuries, held in the left hand in dueling and jused to parry the sword of an opponent. Also called left-hand dagger. [< F: lit., left hand]

main-land (mān/land/, -lənd), n. the principal land sol a country, region, etc., as distinguished from adjacent jelands: the mainland of Greece. [ME; see MAIN', 1.AND] — main/land/er, n.

Main-land (mān/land/, -lənd), n. 1. the largest of the Shetland Islands. 15,172 (1951); ab. 200 sq. ml. 2. ar Fomona (def. 3).

Emain/ line/, 1. a through railroad route: a principal

main/ line/, 1. a through railroad route; a principal filme of a railroad as contrasted with a branch or secondary line. 2. Siang. a. a prominent and readily accessible vein of the body that may be used for a narcotic's injection. b. the act of mainlining.

Main/ Line/, a fashionable residential district west of Philadelphia.

west of Philadelphia.

main-line (mān/lin/, lin/), v.i., -lined, -lin-ing.

Slang. to inject a narcotic, esp. heroin, directly into
the vein. [v. use of Main Line] —main/lin/er, n.

main-ly (mān/lē), adv. 1. chiefly; principally; for
the most part; in the main; to the greatest extent:
Our success was due main; to his efforts. The audience
consisted mainly of students. 2. Obs. greatly; abundantly. [ME maynitche, maynly. See Main!, -LY]
main-mast (mān/mast/, māst/, Naul. mān/məst), n.

Naul. 1. the second mast from forward in any vessel
baving two or more masts, except for a yawl, ketch,
or dandy. See illus under quarter deck. 2. the larger
forward mast of a yawl, ketch, or dandy. 3. the sole
mast of any of various vessels, as sloops or cutters.

[Main-unf (mān/nər), n. Old Eng. Law. a stolen article

main-our (mā/nor), n. Old Eng. Law. a stolen article found on the person of or near the thief: to be taken with the mainour. Also, manner. [ME < AF mainour. Gof manoeusre hand labor); see MANEUVER]

mainsiay of the country's economy. [ME; see Main', STAY'2] 1
main' stem', Slang, the main street of a city or 1
town; the main drag.

main.stream (mān'strēm'), n. 1. the principal or 1
dominant course, tendency, or trend: the mainstream
of our nation's history. 2. a river having tributaries.
—adj. 3. of, pertaining to, or characteristic of jazz
falling historically between Dixieland and modern
jazz; specifically, swing music. Cf. traditional (def. 4).
[Main' street', a novel (1920) by Sinclair Lewis.
main.tain (mān tān'). v.t. 1. to keep in existence or
continuance; preserve; retain: to maintain good relations
with Canada. 2. to keep in due condition, operation, or
force; keep unimpaired: to maintain order; to maintain
public highways. 3. to keep in a specified state, position, etc.: to maintain a correct posture. 4. to affirm;
assert; declare: He maintained that the country was
sort downhill. 5. to support in speech or argument,
as a statement, proposition, etc. 6. to keep or hold
against attack: to maintain one's ground. 7. to provide
for the upkeep or support of; carry the expenses of:
He has to maintain a large family on a small salary.
[ME mainteine(n) CoF mainten(r) < LL manil salary.
[ME mainteine(n) CoF mainten(r) < LL manilienere, in
abl. of manus hand (see MANUAL) + tenere to hold
(see renert) — maintain-able, ad; — maintain-fr, n.

—Syn. 1. keep up, continue. 4. aver, asseverate, state,
hold, allege: 5. uphold, defend, vindicate, justify.

7. See support. —Aat. 1. discontinue. 5. contradict.

maintaining a constant force on the going train of a
timepiece as to is being wound.

main-tain-or (mān tā'nər), n. Law. one guilty of
maintaining a constant force on the going train of a
timepiece as to is being wound.

maintenance. [ME meyntenour < AF. See MAINTAIN, on?] tenance (mān/t³nons), n. 1. act of maintaining: The apartment was too expensive for easy maintenance. 2. state of being maintained: The maintenance of friendly relations with England has always been important. 3. means of upkeep, support, or subsistence; livelihood: The widow was left with sufficient maintenance. 4 Law, an officious meddling in a suit in which the meddler has no interest, by assisting either party with means to prosecute or defend it. [ME maintenance < MF maintenance. See MAINTAIN, ANCE]—Syn. 3. See living.

main/tenance and cure/, Law, the right of an injured seaman to support and medical treatment. main/tenance of mem/bership, an arrangement or agreement between an employer and a labor union by which employees who are members of the union at the time the agreement is made, or who subsequently join, must either remain members until the agreement expires, or be discharged.

Main-tenon (mant) non', n. Marquise de (Francoise d'Aubigné), 1835-1719, second wife of Louis XIV, main-top (mān/top/), n. Naul. a platform at the

Main-top (man/top/), n. Naut. a platform at the head of the lower mainmast. [ME; see MAIN¹, Top¹] main-top-gal·lant (man/top-gal/ant; Naut. man/to-gal/ent), n. the main-top-gallantmast, its sail, or its yard. See illus. under sail.

yard. See ilius. under sail.

main-top gallantmast (mān/top gal/ant mast/,
-mist/; Naul. mān/to gal/ont mast), n. Naul. the
mast next above the main-topmast.

main-top-mast (mān/top/mast/, -mäst/; Naul. mān/top/mast), n. Naul. the mast next above the main
lower mast.

Mai-son de Mo-lière, La (Fr. la me zôn/ de mô-lver/). See Comédie Française.

mai-son de san-té (me zôn do san tê/), pl., mai-sons de san-té (me zôn do san tê/). French, a private hospital or sanitarium for the sick or insane. [lit., house of health]

lit., house of health]

mai-son-ette (mš/zə net'), n. Chiefly Brit. a small
apartment, esp. part of a private house rented as an
apartment. Also, mai/son-nette', [< F, OF, equiv. to
maison house (see mansion) + -elle-ette]

maist (mäst), adi, n., adv. Scol. and North Eng. most.

mai-thu-na (mi/tōo na), n. Hinduism. sexual intercourse, when regarded as taboo.

Mait-land (māt/lond), n. 1. Fredrick William,
1850-1906, English jurist and legal historian. 2. a
town in central Florida. 3570 (1980).

mai-tre d' (mā/tər dē/, mā/trə-), pl. mai-tre d's.
Informal. See maitre d'hôtel (defs. 1-3).

mai-tre de ballet (Fr. me/ta² də balā/), pl.

tel', ma'troz; Fr. me'tra do tel'). 1. a steward or butler. 2. a headwaiter. 3. the owner or manager of a hotel. 4. Cookery, a sauce of melted butter, minced parsley, and lemon juice or vinegar. [< F: master of (the) hotel]

maize (māz), n. 1. (chiefly in British and technical usage) corn' (def. 1). 2. a pale yellow resembling the color of corn. —adj. 3. of the color of maize. [< Sp. maiz < Hispaniolan Taino mahis]

maize/ oil/. See corn oil.

maize oil. See corn oil.

Maj., Major.

Ma-jes-ta (ma jes-ta), n. a girl's given name.

ma-jes-ta (ma-jes-ta), n. a girl's given name.

MAJEST(Y) + 1cl — ma-jes-ta-ta-ly, adv.

—Syn. august. splendid, magnificent, regal, royal, kingly, imperial, noble, lofty. —Ant. base, mean.

mai-es-ty (maj/i stē), n. pl. -ties. 1. regal, lofty, or stately dignity; imposing character; grandeur: majesty of bearing. 2. supreme greatness or authority; sover-seignty: All paid tribute to the majesty of Rome. S. a royal personage, or royal personages collectively: The royal wedding was attended by the majesties of Europe. 4. (usually cap.) a title used when speaking of or to a sovereign (usually prec. by his, her, or your): His Majesty's Navy; Will your Majesty hear our petitions' 5. Christ in Majesty, a representation of Christ as ruler of the universe. [ME majeste < MF et al-gestal's (s. of majestās) sovereignty, greatness, grandeur, equiv. to *mājes- (akin to mājus; see Major) + -tāl--ry²]

Maj. Gen., Major General.

Maj. Gen., Major General.

ma-jol-i-ca (ma jol/a ka, ma yol/-), n. 1. Italian earthenware covered with an opaque glaze of tin oxide; falence; delft. Also, majolica. [earlier majolica clarifer majolica companies compa

and usually linguity metonated and usually linguity metonated and lateral having an opaque glaze of tin oxide; faience; delit. Also, maiolica. [earlier maiolica < 1t < ML, var. of LL Mājorica Mlaorota, where it was made]

ma.jor (mā/jər), n. 1. Mītl. a commissioned officer ranking next below a lieutenant colonel and next above a captain. 2. one of superior rank, ability, etc., in a specified class: Minors outnumber majors in most fields of endeavor. 3. a subject or field of study chosen by a student to represent his principal interest and upon which he concentrates a large share of his efforts: History was his major at college. 4 a person of full legal age (opposed to minor). 5. Music. a major interval, chord, scale, etc. 6. the majors, Spotts, the major leagues: He coached in the majors as well as in the minors. —adf. 7 greater, as in size, amount, extent, importance, rank, etc.: the major part of the town. 8. 7 great, as in rank or importance: a major quistin; a major artist. 9. of or pertaining to the majority; the major opinion. 10. of full legal age. 11. Music. a. (of an interval) being between the tonic and the second, third, sixth, and seventh degrees of a major scale: the major intrid. The major sixth, b. (of a chord) having a major third between the root and the note next above it. 12. (cap.) (of one of two male students in the above it. 12. (cap.) (of one of two male students in mot of a scientific bent. 13. pertaining to the subject in which a student takes most of his courses: His major field is english history. —v.i. 14. to follow a major course of study: He is majoring in the physical sciences. [< L, comp. of magnus great; r. ME majour < AF]
—Syn. 8. See capital.

Major ca (majōr/ko, -yōr/-), n. a Spanish island in the Wediterranean: the largest of the Balearic Islands. 328,000 (est. 1954); 1405 sq. mi. Cap.: Palma. Spanish, Mailorca. —Major/can, adi., n.

major-do-mo (mā/jər dō/mō), n., pl. -mos. 1. a mayordomo < LL majordomūs head of the house, equiv. to major mazor mayordomo + domūs, gen. of do

top/most), n. Naul. the mast next above the main lower mast.

main-top-sail (mān/top/sāl/; Naul. mān/top/sal), n. Naul. a topsail set on the mainmast.

main-top-sail schooner, Naul. a two-masted or three-masted schooner having square topsails on the foremast and mainmast: a jackass brig or jackass bark. Also called two-topsail schooner.

Main/-try/sail schooner having square topsails on the foremast and mainmast: a jackass brig or jackass bark. Also called two-topsail schooner.

Main/-try/sail rig/ (mān/tr/sal, -sāl/), Naul. See wishbone rig.

main/-top-sail schooner.

Main/-try/sail rig/ (mān/tr/sal, -sāl/), Naul. See wishbone rig.

main/-top-sail schooner.

Main/-top-sail schooner.

Main/-top-sail schooner.

Main/-try/sail rig/ (mān/tr/sal, -sāl/), Naul. See drum majorette.

[DRUM] MAJOR + -zrvz]

ma-jor-ette (mā/jardomus head of the house, equiv.

ma-jor-ette (mā/jaret/), n. See drum majorette.

[DRUM] MAJOR + -zrvz]

[DRUM] MAJOR + -zrvz]

ma-jor-ette (mā/jaret/), n. See drum majorette.

[DRUM] MAJOR + -zrvz]

[DRUM] MAJOR + -zrvz]

ma-jor-ette (mā/jaret/), n. See drum majorette.

[DRUM] MAJOR + -zrvz]

[DRUM] MAJOR + -zrvz]

ma-jor-ette (mā/jaret/), n. See drum majorette.

[DRUM] MAJOR + -zrvz]

[DRUM] MAJOR + -zrvz]

ma-jor-ette (mā/jaret/), n. See drum majorette.

[DRUM] MAJOR + -zrvz]

[DRUM] MAJOR + -zrvz]

ma-jor-ette (mā/jaret/), n. See drum majorette.

[DRUM] MAJOR + -zrvz]

[DRUM] MAJOR + -zrvz]

ma-jor-ette (mā/jaret/), n. See drum majorette.

[DRUM] Major el/ement, Geol. any chemical found in great quantity in the rocks of the earth's crust. Cf. minorette.

[DRUM] Major el/ement, Geol. any chemical general. —marjor-general.cy, marjor-general.sipp', marjor-general.sipp', marjor-general.cy, marjor-ley (marjor-ley (marjor-ley

ma/jor league', 1. either of the two main professional baseball leagues in the U.S. 2. a league of corresponding stature in certain other sports, as ich hockey, football, or basketball.

major-league team. [major le/ger), n. a member of a major-league team. [major leAgue + -ER¹]
major mode, Music. 1. See major scale. 2. See major or/der, Rom. Cath. Ch. the degree or grade of priesthood, diaconate, or subdiaconate. Ct. minor order.

town in central Florida 30/0 (1990).

with the mainour. Also, manner. [ME & AF mainoure with the mainour. Also, manner. [ME & AF mainoure with the mainour. Also, manner. [ME & AF mainoure with the mainour. Also, manner. [ME & AF mainoure with the mainour. Also, manner. [ME & AF mainoure with the mainour. Also, manner. [ME & AF mainoure with the mainour. Also, manner. [ME & AF mainoure with the mainour. Also, manner. [ME & AF mainoure with the mainour. Also, mainoure de (mā/tor dē/, mā/tro-), pl. mai-tre d'so. Alā/), pl. mai-tre d'so. Alā/),

EXHIBIT 11

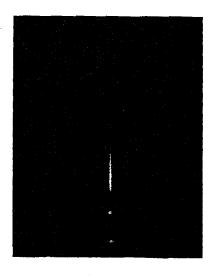
GENERAL **CHEMISTRY**

THIRD·EDITION

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G-16 Glossary

Document 174-2

Simple cubic unit cell a cubic unit cell in which lattice points are situated only at the corners of the unit cell.

Simplest formula see empirical formula.

Single bond a covalent bond in which a single pair of electrons is shared by two atoms.

Single-replacement reaction see displacement reaction.

Sol a colloid that consists of solid particles dispersed in a liquid.

Solid the form of matter characterized by rigidity; a solid is relatively incompressible and has fixed shape and volume.

Solubility the amount of a substance that dissolves in a given quantity of solvent (such as water) at a given temperature to give a saturated solution.

Solubility-product constant (K_{sp}) the equilibrium constant for the solubility equilibrium of a slightly soluble (or nearly insoluble) ionic compound.

Solute in the case of a solution of a gas or solid dissolved in a liquid, the gas or solid; in other cases, the component in smaller amount.

Solution see homogeneous mixture.

Solvay process an industrial method for obtaining sodium carbonate from sodium chloride, ammonia, and carbon dioxide.

Solvent in a solution of a gas or solid in a liquid, the liquid; in other cases, the component in greater amount.

Specific heat capacity (specific heat) the quantity of heat required to raise the temperature of one gram of a substance by one degree Celsius (or by one kelvin).

Spectator ions ions in an ionic equation that do not take part in the reaction.

Spectrochemical series an arrangement of ligands according to the relative magnitudes of the crystal field splittings they induce in the d orbitals of a metal ion.

Spin quantum number (m_s) the quantum number that refers to the two possible orientations of the spin axis of an electron; possible values are $+\frac{1}{2}$ and $-\frac{1}{2}$.

Spontaneous process a physical or chemical change that occurs by itself.

Square pyramidal geometry the geometry of a molecule in which a central atom is at the apex of a pyramid and four other atoms form the square base of the pyramid.

Square planar geometry the geometry of a molecule in which a central atom is surrounded by four other atoms arranged in a square and in a plane containing the central atom.

Stability constant (of a complex) see formation constant.

Standard electrode potential (E°) the electrode potential when the concentrations of solutes are 1 M, the gas pressures are I atm, and the temperature has a specified valueusually 25°C.

Standard emf (E_{cell}°) the emf of a voltaic cell operating under standard-state conditions (solute concentrations are 1 M, gas pressures are 1 atm, and the temperature has a specified value—usually 25°C).

Standard enthalpy of formation (standard heat of formation), ΔH_f° the enthalpy change for the formation of one mole of the substance in its standard state from its elements in their reference forms and in their standard states.

Standard entropy (S) the entropy value for the standard state of a species.

Standard free energy of formation (ΔG_t) the free-energy change that occurs when one mole of substance is formed from its elements in their stablest states at 1 atm and at a specified temperature (usually 25°C).

Standard heat of formation see standard enthalpy of formation.

Standard potential diagram a convenient graphical presentation of the standard potentials of an element.

Standard state the standard thermodynamic conditions (1 atm and usually 25°C) chosen for substances when we are listing or comparing thermochemical data.

Standard temperature and pressure (STP) the reference conditions for gases, chosen by convention to be 0°C and 1 atm.

State function a property of a system that depends only on its present state, which is determined by variables such as temperature and pressure, and is independent of any previous history of the system.

States of matter the three forms that matter can assumesolid, liquid, and gas.

Steam-reforming process an industrial preparation of hydrogen and carbon monoxide mixtures by the reaction of steam and hydrocarbons at high temperature and pressure over a nickel catalyst.

Stereoisomers isomers in which the atoms are bonded to each other in the same order but that differ in the precise arrangement of these atoms in space.

Stock system a system of chemical nomenclature in which the charge on a metal atom or oxidation number of an atom is denoted by a Roman numeral in parentheses following the element name.

Stoichiometry the calculation of the quantities of reactants and products involved in a chemical reaction.

Stratosphere the region of the atmosphere that lies just above the troposphere and wherein the temperature increases with increasing altitude.

Strong acids an acid that ionizes completely in water.

Strong base a base that is present in aqueous solution entirely as ions, one of which is OH-.

Strong electrolyte an electrolyte that exists in solution almost entirely as ions.

EXHIBIT 12

(12) United States Patent Albert et al.

Document 174-2

(10) Patent No.:

US 7,108,866 B1

(45) Date of Patent:

Sep. 19, 2006

(54) CHRONOTHERAPEUTIC DILITIAZEM FORMULATIONS AND THE ADMINISTRATION THEREOF

(75) Inventors: Kenneth Stephen Albert, Mt. Kisco, NY (US); Paul José Maes, Oakville

(73) Assignee: Biovall Laboratories International SRL, St. Michael (BB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 09/567,451

(22) Filed: May 8, 2000

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/465,338, filed on Dec. 17, 1999, now abandoned.

(30) Foreign Application Priority Data

(51)	Int. Cl.	
	A61K 9/22	(2006.01)
	A61K 9/26	(2006.01)
	A61K 9/48	(2006.01)
	A61K 9/50	(2006.01)
	A61K 9/52	(2006.01)

See application file for complete search history.

(56) References Cited

U.S. PATENT DOCUMENTS

4,263,273 A 4/1981 Appelgren et al. 424/21

(Continued)

FOREIGN PATENT DOCUMENTS

0 149 920 A2 12/1984

(Continued)

OTHER PUBLICATIONS

Klokkers-Bethke, K. et al., "Development of a multiple unit drug delivery system for positioned release in the gastrointestinal tract", Journal of Controlled Release, 15 (1991) 105-112.

(Continued)

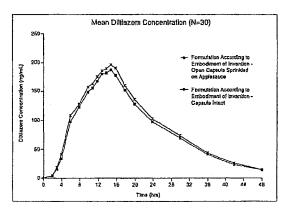
Primary Examiner—S. Tran (74) Attorney, Agent, or Firm—Hunton & Williams; Robin L. Teskin

57) ABSTRACT

A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg or more (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a C_{max} of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

- (i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
- (ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria.

88 Claims, 15 Drawing Sheets



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				****	D
U.S. PALENI	DOCUMENTS		5,622,716 A		Barth
4,696,924 A 9/1987	Marcoux 514/211		5,626,860 A	5/1997	
4,705,695 A 11/1987			5,654,005 A	8/1997	
	Panoz et al 424/459		5,662,933 A	9/1997	
			5,667,801 A	9/1997	
	Stephens et al		5,670,168 A	9/1997	
			5,670,172 A	9/1997	Buxton et al 424/495
	Ventouras 424/468		5,681,583 A	10/1997	
	Howard et al 424/475		5,688,794 A	11/1997	Meier et al 514/250
4,808,413 A 2/1989		5	5,716,933 A	2/1998	Meier et al 514/12
4,824,678 A 4/1989		:	5,716,962 A	2/1998	
4,832,958 A 5/1989			5,736,159 A	4/1998	Chen et al 424/480
	Colombo et al 424/482	5	5,756,513 A		Cincotta et al 514/288
4,859,469 A 8/1989		:	5,773,025 A	6/1998	Baichwal 424/458
4,859,470 A 8/1989			5,785,994 A	7/1998	Wong et al 424/473
4,880,631 A 11/1989		I	RE35,903 E	9/1998	Debregaes et al 424/458
4,891,230 A 1/1990		:	5,830,503 A	11/1998	Chen 424/480
	Geoghegan et al 424/497		5,834,023 A	11/1998	Chen 424/497
4,917,899 A 4/1990	Geoghegan et al 424/461		5,834,024 A	11/1998	Heinicke et al 424/497
4,938,967 A 7/1990	Newton et al 424/458		5,837,379 A	11/1998	Chen et al 424/465
4,940,588 A 7/1990	Sparks et al 424/490	4	5,840,329 A	11/1998	Bai 424/458
4,952,402 A 8/1990	Sparks et al 424/419		5,843,347 A	12/1998	Nguyen et al 264/9
	Debregeas et al 424/458		5,846,563 A	12/1998	
4,966,769 A 10/1990	Guittard et al 424/473		5,851,555 A	12/1998	
5,000,962 A 3/1991	Sangekar et al 424/482		5,869,097 A	2/1999	
5,002,776 A 3/1991	Geoghegan et al 424/497		5,914,134 A	6/1999	
5,004,614 A 4/1991	Staniforth 424/466		5,916,595 A	6/1999	
5,008,114 A 4/1991	Lovrecich 424/484		5,922,352 A	7/1999	Chen et al 424/465
5,051,262 A 9/1991	Panoz et al 424/468		5,945,125 A	8/1999	
5,055,306 A * 10/1991	Barry et al 424/482		5,958,456 A	9/1999	Baichwal et al 424/489
5,082,668 A 1/1992	Wong et al 424/473		5,004,582 A	12/1999	Faour et al 424/473
5,112,621 A 5/1992	Stevens et al 424/497		5,022,562 A	2/2000	Autant et al 424/489
5,149,542 A 9/1992	Valducci 424/493			3/2000	Heinicke et al
5,156,850 A 10/1992	Wong et al 424/473		5,033,687 A	312000	Hemicke et al 424/497
5,160,744 A 11/1992	Jao et al 424/473				
5,175,003 A 12/1992	Goldman 424/484		FOREIG	n pate	NT DOCUMENTS
5,178,867 A 1/1993	Guittard et al 424/473				
5,190,765 A 3/1993	Jao et al 424/473	EP		DR3 A1	9/1987
5,219,621 A 6/1993	Geoghegan et al 424/462	EP		698 A	1/1988
5,229,135 A 7/1993		EP	0 309	051 A1	9/1988
5,252,338 A 10/1993		EP	0 320	097 Al	10/1988
5,260,068 A 11/1993		EP	0 856	313 A1	10/1988
5,260,069 A 11/1993	Chen 424/451	EP	0 315	414 A1	11/1988
5,275,824 A 1/1994	Carli et al 424/490	EP	0 318	398 Al	11/1988
5,286,497 A * 2/1994	Hendrickson et al 424/490	EP	0 322	277 Al	12/1988
	Deboeck et al 424/497	EP		105 A1	4/1989
	Wright et al 424/473	EP		106 A1	5/1989
	Baichwal 424/469	EP		417 A1	11/1989
5,336,504 A 8/1994		EP		174 A	12/1993
5,344,657 A 9/1994		EP			
5,354,556 A 10/1994				637 BI	4/1998 * 8/1998
5,364,620 A 11/1994		EP	0856		0.1770
5,419,917 A 5/1995		EP		945 BI	6/1999
	Hendrickson et al 424/490	EP		424 BI	9/1999
	Paradissis et al 424/480	wo	WO 90/06		6/1990
	Lovrecich 424/489	WO	WO 91/01		2/1991
	Baichwal 424/457	wo	WO 93/0		1/1993
	Chen et al 424/464	WO	WO 9300	093 AI	* 1/1 9 93
	Chen 424/464	WO	WO 93/09	767	5/1993
	Conte et al 424/480	WO	WO 96/29	992	10/1996
	Hendrickson et al 424/490	wo	WO 97/23	219	7/1997
5,472,708 A 12/1995		WO	WO 97/48		12/1997
5,472,711 A 12/1995		WO	WO 98/32		7/1998
	Baichwal et al 424/485	WO	WO 98/33		8/1998
	Chen	WO	WO 98/33		8/1998
	Baichwal 424/451		0 5 0 5 5		
	Eichel et al 424/480		OP7	יים מיוד	DI 1C ATIONE
	Deboeck et al 424/494		OH	ick PU	BLICATIONS
	Baichwal 424/488	Deedy	anian Catal I	Effect of 1	Morning Versus Evening Dosing of
5,558,879 A 9/1996					nia Detected by Ambulatory Elec-
5,567,441 A 10/1996					Chronic Stable Angio Pectoris, Pra
	Buxion et al				Cardiology, vol. 80, Aug. 15, 1997,
5,616,345 A 4/1997		p. 421			
0 10 10 10 FL -# 1937	Engline of the mount of the 1971	P			

US 7,108,866 B1

Page 3

Kelly, J.G. et al., Pharmacokinetic Properties and Antihypertensive Efficacy of Once-Daily Diltiazem, Journal of Cardio-Vascular Pharmacology, 17:6:957-963, (1991).

Kohno, I. et al., Administration Time—Dependent Effects of Diltiazem on The 24-Hour Blood Pressure Profile of Essential Hypertension Patients, Chronobiology International, 14(1), 71-84, (1997).

Leeuwenkamp, O.R. et al, A comparative study of the steady-state pharmacokinetics of immediate-release and controlled-release diltiazem tablets, Eur. J. Clin. Pharmacol, (1994) 46:243-247.

Thiffault, J. et al., The Influence of Time Administration on the Pharmacokinetics of a Once A Day Diltiazem Formulation: Morn-

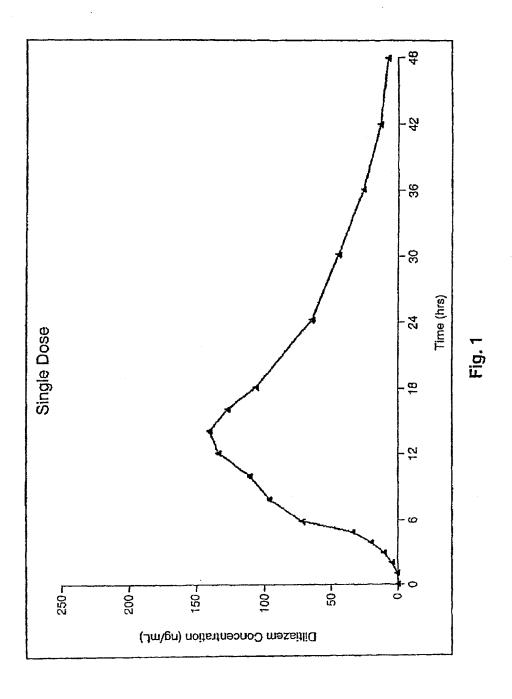
Pharmacokinetics of a Once A Day Diffuzzem Formulation: Morning Against Bedtime, Biopharmaceutics & Drug Disposition, vol. 17, 107-115 (1996).

Zahirul, M. et al., Recent Trends and Progress in Substained or Controlled Oral Delivery of Some Water Soluble Drugs; Morphine Salts, Dilitazem and Captopril, Drug Development and Industrial Pharmacy, US, New York, NY, vol. 21, No. 9, Jan. 1, 1995, pp. 1037-1070 1037-1070.

* cited by examiner

Sep. 19, 2006

Sheet 1 of 15

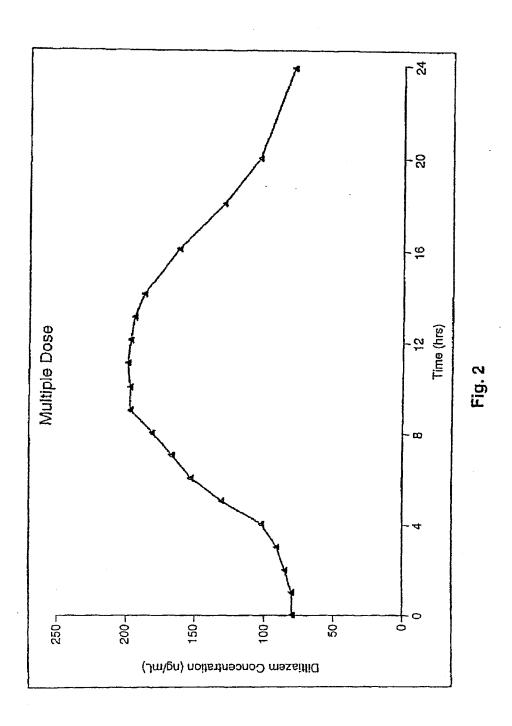


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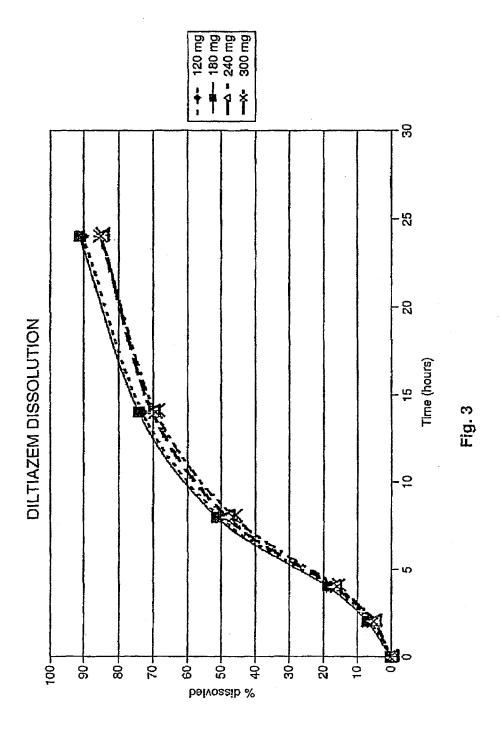
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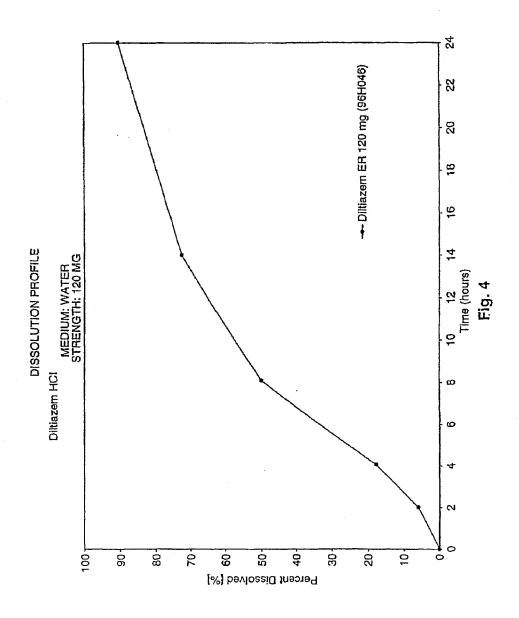
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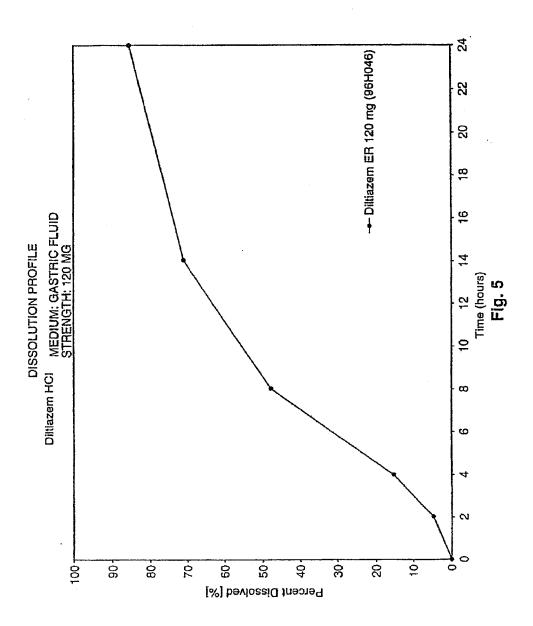
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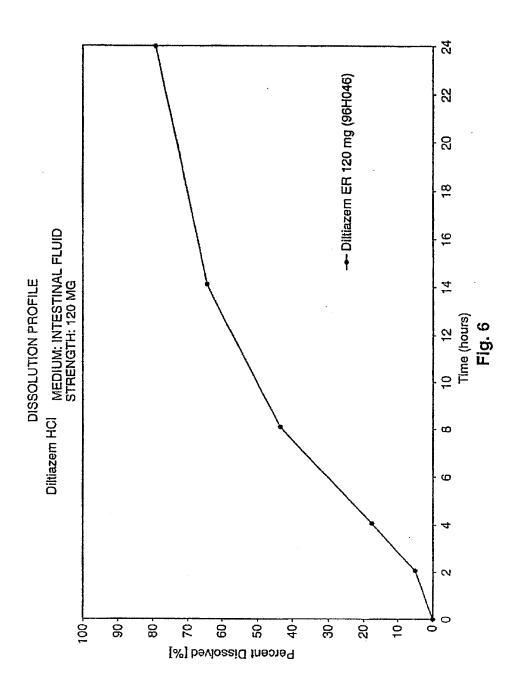
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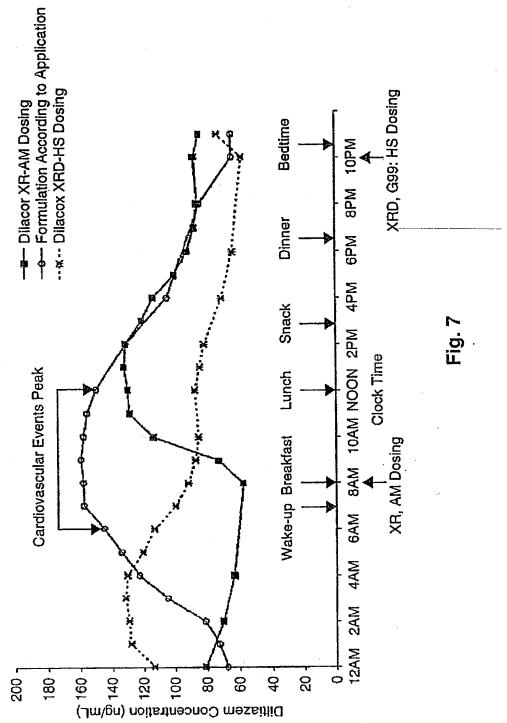
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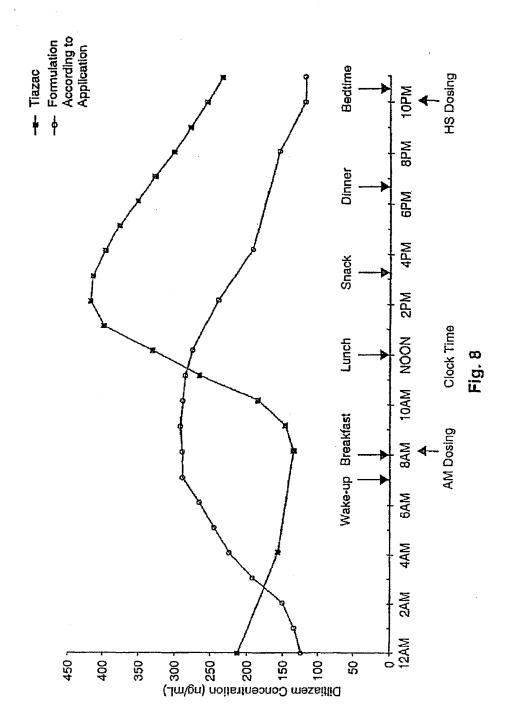
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U.S. Patent

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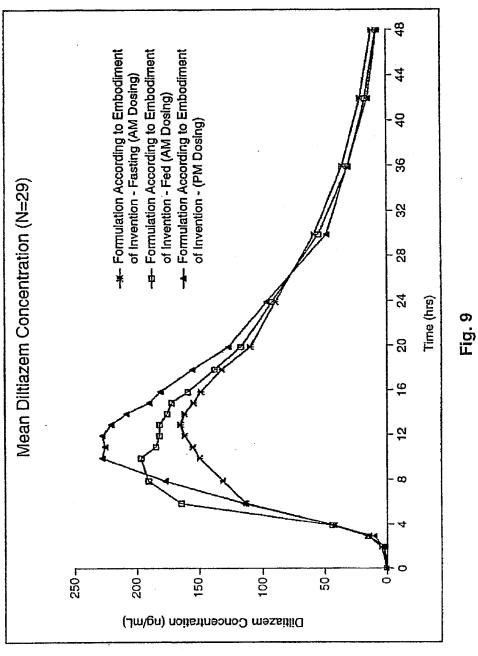
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Dilitazom AUCt PK Summary

	For	mulation A	ecording to	Embodimer	it of Invent	on		
							Morning	
	Morning			ng Fed		Dosing		Night/Morning
Subject	AUCI	Log AUCI		Log AUCI	AUCI	Log AUCt	Ratio	Ratio
Ž	1730.75	7.46	2647.15	7.88	1987.11	7.59	1.53	1.15
3	2712.98	7.91	2336.67	7.76	3249.94	8.09	0.86	1.20
4	2688.34	7.90	1907.61	7.55	2892.21	7.97	0.71	1.08
5	4192.37	8.34	4108.85	8.32	4702.33	8.46	0.98	1,12
6	3074.51	8.03	2887.98	7.97	3900.06	8,27	0.94	1,27
7	1629.81	7.40	1847,56	7.52	2723.36	7.91	1.13	1.67
8	841.10	6.85	1970.97	7.59	1835.11	7.51	2.09	1.95
9	3144.13	8.05	3462.59	8.15	2923.85	7.98	1.10	0.93
10	2074.94	7.64	2997,45	8.01	4028.83	8.30	1.44	1.94
11	3553.96	8.20	2771.53	7.93	3454.72	8.15	0.76	0.95
12	2584.22	7.90	3790.43	8.24	3141.47	8.05	1,41	1.17
13	3352.69	8.12	3751.95	8.23	3708.83	8.22	1.12	1,11
14	2988.61	6.00	3665.60	8.21	3141.05	8.05	1.23	1.05
15	6796.97	8.82	8204.22	9.01	7578.33	8.93	1.21	1.11
16	2873.70	7.96	4644.79	8.44	4192.09	8.34	1.62	1.46
17	4468,33	6.40	4222.55	8.35	3762.50	8.23	0.94	0.84
18	5654.29	8.64	5635.72	B.64	7159.38	8.88	1.00	1.27
19	4944.07	8.51	5107.44	8.54	4812.20	8.48	1.03	0.97
20	2086.73	8.00	2988,34	8.00	2791.23	7.93	1.00	0.93
21	2908.88	7.98	3314.12	B.11	4389.98	8.39	1.14	1.51
22	4270.43	8.36	3790.06	· 8.24	3631,01	8.20	0.89	0.85
23	6150.18	8.72	6092.56	8.71	7478.22	8.92	0.99	1.22
25	2926.45	7.98	5633,64	8.64	4639.10	8.48	1.93	1.65
26	3928.61	8.28	4614,43	8.44	4359.77	8.38	1.17	1.11
27	3637.94	8.20	4587,48	8.43	4063.15	8.31	1.26	1.12
28	4177.76	8.34	4945.31	8.51	6689.14	8.81	1.18	1.60
29	3609.69	8.19	2720.67	7.B1	2163.20	7.68	0.75	0.60
30	4483,17	8.41	5222.54	8.56	5587.50	8.63	1.16	1.25
32	4058.04	8.31	3531,47	8.17	3082.87	8.03	0.87	0.76
Mean	3542.88	8.10	3910.40	8,21	4078.57	8.25	1,15	1.20
SD ·	1304.23	0.41	1431.24	0.36	1554.69	Ó.37	0.33	0.33
CY	36.81	5.08	36.60	4.43	38.12	4.46	28.23	27.33
Medlan	3352.69	8.12	3751.95	8.23	3762.50	8.23	1.12	1.12
Geo Mean	3292.83	8.09	3671.24	8.20	3818.30	5.24	1.11	1.16
Fed/Fastin	Ratio (Mo	ming Dos	ing)		NightMo	ming Ratio		
Ratio of Me	ans	1.10	#		Ratio of F	deans	1.15	
Ratio of Ge	o Means	1.11	#		Ratio of C	Seo Means	1.16	
Avg of Indi	vidual Rati	1.15	#		Avg of in	dividual Ratios	1,20	

Fig. 9A

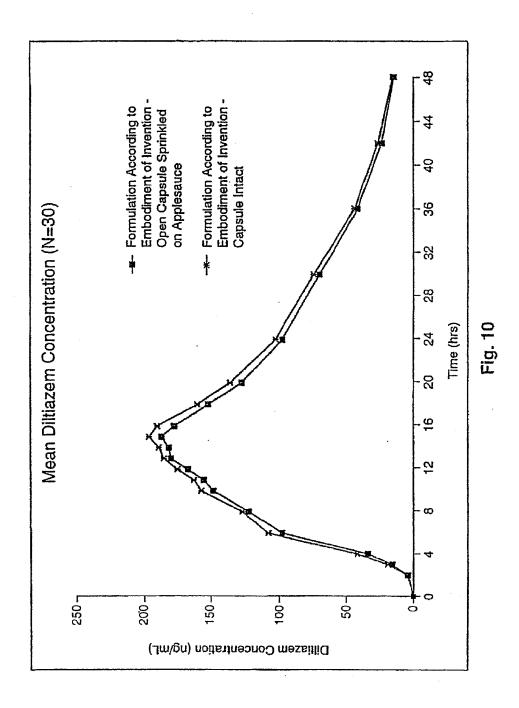
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1 Crimax Timax Grisis Log Crimax Timax Grisis Log Crimax A 486 100 18777 5.23 11.0 14.284 4.87 4.897 4.89 10.0 18.04 6.26 6.54 6.89 10.0 18.08 4.78 10.0 18.144 6.26 6.19 4.51 11.0 18.20 4.78 10.0 18.144 6.26 6.19 6.20 14.0 18.20 14.0 18.20 14.0 18.20 14.10 18.20 14.0 14.0 14.0 14.0 14.0 14.0 14.0 14.	Comean Trans. Crist. Log Crist. Trans. Crist. Log Crist. Scale 155 4510 1500 1500 1500 1500 1500 1500		2	Moreing Fasting	, ga		Momina Fed	73	-	Night Doging	•	FedFast	Moming FedFast Night/Moming
100 18771 523 143 14384 4.87 150	100 18771 523 130 143.84 487 140 187 130 143.84 487 140 143.84 140 143.84 140 143.84 140 143.84 140 143.84 140 143.84 140 143.84 140 143.84 140 143.84 14	Cultiple	Tmay	Cm	Loo Cmax	Tmax	Cmex	Log Cmitt		Contra	Log Cmax	Ratio	Ratio
11.0 122,04 4,81 10.0 234,557 5,51 0.90 12.0 118,68 4,78 10.0 191,44 5,25 0.08 12.0 124,14 5,10 124,48 5,25 0.08 13.1 14,0 171,04 4,80 12,0 178,67 5,19 1.08 14.0 171,04 4,80 12,0 178,67 5,19 1.08 15.0 126,41 5,10 175,62 5,17 1.08 15.0 126,41 5,10 14,0 175,62 5,17 1.08 15.0 222,70 5,80 12,0 175,62 5,17 1.08 15.0 221,43 5,31 11,0 174,85 5,16 1.71 15.0 221,43 5,31 11,0 174,85 5,16 1.71 15.0 224,82 5,29 13,0 187,32 5,23 1.71 15.0 224,82 5,50 14,0 203,41 5,37 1.09 15.0 224,82 5,57 13,0 236,10 5,32 1.09 15.0 234,82 5,57 13,0 236,10 5,46 1.16 15.0 234,82 5,57 13,0 236,10 5,46 1.16 15.0 234,82 5,57 13,0 236,10 5,46 1.16 15.0 234,82 5,57 13,0 236,10 5,51 1.14 15.0 234,82 5,57 13,0 236,10 5,51 1.14 15.0 234,83 5,33 10,0 236,12 5,51 1.14 15.0 234,83 5,33 11,0 236,14 5,51 1.14 15.0 234,83 5,33 11,0 236,14 5,51 1.14 15.0 234,83 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53 5,33 11,0 236,14 5,51 1.14 15.0 234,53	110 120,04 4,81 10,0 246,57 5,51 0,90 100 196,68 4,78 10,0 196,44 5,25 0,08 101 195,68 4,78 10,0 196,44 5,25 0,08 102 196,41 5,10 12,0 178,67 5,19 1,08 103 195,68 5,26 12,0 178,67 5,19 1,08 104 121,04 4,80 12,0 178,67 5,19 1,08 105 195,70 5,68 12,0 175,52 5,17 1,08 105 195,70 5,68 12,0 175,52 5,17 1,08 105 195,71 5,48 5,04 10,0 195,66 5,21 1,09 105 195,71 5,54 10,0 195,66 5,21 1,09 105 105 105,71 5,54 10,0 105,72 5,23 1,09 105 246,22 5,73 10,0 175,72 5,23 1,09 105 246,22 5,73 10,0 175,73 5,71 1,09 105 246,22 5,73 10,0 175,73 5,71 1,09 105 246,22 5,73 10,0 175,73 5,71 1,09 105 275,76 5,74 10,0 175,73 5,71 1,09 105 275,76 5,74 10,0 175,73 5,71 1,09 105 275,76 5,74 10,0 175,73 5,71 1,09 105 275,76 5,74 10,0 275,72 5,74 1,09 105 275,76 5,74 10,0 275,72 5,74 1,09 105 275,76 5,74 10,0 275,72 5,74 1,09 105 275,76 5,74 10,0 275,72 5,74 1,09 105 275,76 5,74 10,0 275,72 5,74 1,09 105 275,76 5,74 10,0 275,72 5,74 1,09 105 275,76 5,74 10,0 275,72 5,74 1,09 105 275,76 5,74 10,0 275,72 5,74 1,00 105 275,76 5,74 10,0 275,72 5,74 1,00 105 275,76 5,74 10,0 275,72 5,74 1,00 105 275,76 5,74 10,0 275,72 5,74 1,00 105 275,76 5,74 10,0 275,72 5,74 1,00 105 275,76 5,74 10,0 275,72 5,74 1,00 105 275,76 5,74 10,0 275,72 5,74 1,00 105 275,76 5,74 10,0 275,72 5,74 1,00 105 275,76 5,74 10,0 275,72 5,74 1,00 105 275,76 5,74 10,0 275,72 5,74 1,00 105 275,76 5,74 10,0 275,72 5,74 1,00 105 275,76 5,74 10,0 275,72 5,74 1,00 105 275,76 5,74 10,0 275,	2	10.0	88.83	4.59	10.0	187,71	5.23	13.0	143.84	4.97	06'1	1.48
10.0 118.88 4.78 10.0 101.44 5.25 0.58 4.1 10.1 10.1 10.1 10.1 10.1 10.1 10.1 5.1 10.0 10.2 10.2 10.2 10.2 10.2 5.1 10.0 10.2 10.2 10.2 10.2 10.2 5.2 14.0 110.2 10.2 10.2 10.2 10.2 5.2 14.0 110.2 10.2 10.2 10.2 10.2 5.2 10.0 10.2 10.2 10.2 10.2 5.2 10.0 10.2 10.2 10.2 10.2 5.2 10.0 10.2 10.2 10.2 10.2 5.3 10.0 20.1.4 5.3 10.0 20.1.4 5.4 10.0 20.1.4 5.3 10.0 20.1.4 5.5 10.0 20.1.4 5.3 10.0 20.1.4 5.5 10.0 20.1.4 5.3 10.0 20.1.4 5.5 10.0 20.1.4 5.3 10.0 20.1.4 5.5 10.0 20.1.4 5.3 10.0 20.1.4 5.5 10.0 20.1.4 5.3 10.0 20.1.4 5.5 10.0 20.1.4 5.3 10.0 20.1.4 5.5 10.0 20.1.4 5.3 10.0 20.1.4 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1.4 5.3 10.0 5.5 10.0 20.1 10.0 20.1 10.0 5.5 10.0 20.1 10.0 20.1 10.0 5.5 10.0 20.1 10.0 20.1 10.0 5.5 10.0 20.1 10.0 20.1 10.0 5.5 10.0 20.1 10.0 20.1 10.0 5.5 10.0 20.1 10.0 20.1 10.0 5.5 10.0 20.1 10.0 20.1 10.0 5.5 10.0 20.1 10.0 20.1 10.0 5.5 10.0 20.1 10.0 20.1 10.0 5.5 10.0 20.1 10.0 20.1 10.0 5.5 10.0 20.1 10.0 20.1 10.0 5.5 10.0 20.1 10.0 20.1 10.0 5.5	100 118.88 4.78 100 191.44 5.25 0.08 0.08 14.0 191.40 191.40 192.0 194.98 5.54 0.08 15.1 192.0 194.98 5.54 0.08 15.1 192.0 195.98 5.54 0.08 15.1 192.0 195.98 5.10 195.90	•	130	138.18	4.91	11.0	123.04	4.81	10.0	246.57	5.51	0.00	1,81
1,	1, 0, 195,86 5.26 12,0 254,86 5.54 0.08 14,0 119,30 4.76 12,0 178,67 5.19 1.05 14,0 119,30 4.76 12,0 178,67 5.19 1.05 15,0 212,70 5.16 12,0 178,67 5.19 1.05 15,0 212,70 5.16 12,0 178,67 5.17 1.05 15,0 201,43 5.17 11,0 174,86 5.21 1.71 15,0 201,43 5.24 10,0 208,76 5.23 1.47 15,0 202,25 5.20 13,0 107,22 5.23 1.47 15,0 204,82 5.57 13,0 107,22 5.23 1.47 15,0 204,82 5.57 13,0 107,22 5.23 1.47 15,0 204,82 5.57 13,0 178,76 5.17 1.05 15,0 204,82 5.57 13,0 178,76 5.17 1.05 15,0 204,82 5.25 13,0 271,89 5.47 1.16 15,0 207,18 5.23 10,0 271,49 5.47 1.16 15,0 207,18 5.23 10,0 271,49 5.47 1.16 15,0 207,18 5.23 10,0 271,49 5.47 1.16 15,0 207,18 5.23 10,0 271,49 5.47 1.16 15,0 207,18 5.23 10,0 271,49 5.47 1.16 15,0 207,18 5.23 11,0 271,49 5.44 1.16 15,0 207,18 5.23 11,0 271,49 5.44 1.16 15,0 207,18 5.23 11,0 271,49 5.44 1.16 15,0 207,18 5.23 11,0 271,49 5.44 1.16 15,0 207,18 5.23 11,0 271,49 5.44 1.16 15,0 207,18 5.23 11,0 271,49 5.44 1.16 15,0 207,18 5.23 11,0 271,49 5.44 1.16 15,0 207,18 5.23 11,1 4.08,78 5.44 1.16 15,0 207,18 5.23 11,1 4.08,78 5.44 1.16 15,0 207,18 5.23 11,1 4.08,78 5.44 1.16 15,0 207,18 5.23 11,1 4.08,78 5.44 1.16 15,0 207,18 5.23 11,1 4.08,78 5.44 1.16 15,0 207,18 5.23 11,1 4.08,78 5.44 1.16 15,0 207,18 5.23 11,1 4.08,78 5.44 1.16 15,0 207,18 5.23 11,1 4.08,78 5.44 1.16 15,0 207,18 5.23 11,1 4.08,78 5.44 1.16 15,0 207,18 5.23 11,1 4.08,78 5.44 1.16 15,0 207,18 5.23 11,1 4.08,78 5.44 1.16 15,0 207,18 5.23 11,1 4.08,78 5.44 1	• •	15.0	133.23	4.89	0,0	118,68	4.78	10.0	191,44	5.25	88.0	1.44
10	1.00 16.41 5.10 178.67 6.19 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1	- W	80	22.52	5.41	8.0	195,66	5.28	12.0	254,96	£,5;	0.88	1.15
5.1 (4.0) (2.1.64) 4.80 12.0 178.87 5.18 1.34 1.18 6.10 122.0 13.05 4.89 1.62 1.75 1.05 6.0 15.30 4.78 11.0 13.56 5.21 1.75 1.05 6.0 16.31 5.12 14.0 18.89 5.23 1.75 1.05 15.464 5.04 14.0 18.89 5.23 1.75 1.89 1.75 1.01 15.464 5.04 14.0 18.89 5.23 1.75 1.89 1.75 1.89 1.75 1.89 1.75 1.89 1.75 1.75 1.89 1.75 <t< td=""><td>\$\begin{array}{c} \text{if } \tex</td><td>· w</td><td>120</td><td>150.95</td><td>5.02</td><td>0.0</td><td>164.11</td><td>5,10</td><td>18,0</td><td>179,67</td><td>5.18</td><td>1.09</td><td>1.19</td></t<>	\$\begin{array}{c} \text{if } \tex	· w	120	150.95	5.02	0.0	164.11	5,10	18,0	179,67	5.18	1.09	1.19
118 11.0 119.30 4.78 11.0 113.13 4.89 162 156 6.0 28270 5.00 13.0 118.62 5.17 1.88 156 6.10 156.81 5.24 13.0 118.50 5.21 1.88 157 10.0 20.143 5.31 11.0 174.85 5.21 1.71 15.0 156.81 5.24 10.0 204.76 5.34 1.70 15.0 15.0 156.81 5.24 10.0 204.76 5.34 1.70 15.0 15.0 25.25 5.24 10.0 204.70 5.46 1.71 15.0 15.0 25.25 5.50 13.0 187.32 5.23 1.72 15.0 25.25 5.50 13.0 187.32 5.23 1.09 15.0 25.25 5.50 13.0 187.32 5.23 1.09 15.0 25.25 5.50 13.0 20.35 1.09 15.0 25.25 5.50 13.0 20.35 1.09 15.0 25.25 5.70 13.0 20.35 1.09 15.0 10.0 26.25 5.70 13.0 20.35 1.09 15.0 10.0 20.75 5.33 13.0 20.32 5.71 15.0 10.0 25.85 5.44 10.0 170.18 5.14 15.0 20.45 5.50 13.0 20.32 5.71 15.0 10.0 25.85 5.44 10.0 170.18 5.14 15.0 20.45 5.20 13.0 20.35 1.09 15.0 20.45 5.30 13.0 20.35 1.30 15.0 20.45 5.30 13.0 20.35 1.30 15.0 20.45 5.30 13.0 20.35 1.30 15.0 20.40 5.32 13.0 20.42 5.89 15.0 20.40 5.32 13.0 20.42 5.89 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.43 5.44 15.0 20.40 5.32 13.0 20.40 5.32 13.0 5.44 15.0 20.40 5.32 13.0 20.40 5.32 13.0 20.40 15.0 20.40 5.32 13.0 20.40 5.32 13.0 20.40 15.0 20.40 5.32 13.0 20.40 5.32 13.0 20.40 15.0 20.40 5.32 13.0 20.40 5.32 13.0 20.40 15.0 20.40 5.32 13.0 20.40 5.32 13.0 20.40 15.0 20.40 5.32 13.0 20.40 5.32 13.0 20.40 15.0 20.40 5.32 13.0 20.40 5.32 13.0 20.40 15.0 20.40 5.32 13.0 20.40 5.32 13.0 20.40 15.0 20.40 5.32 13.0 20.40 5.32 13.0 20.40 15.0 20.40 5.32 13.0 20.40 5.32 13.0 20.40 15.0 20.40 5.32 13.0 20.40 5.32 13.0 20.40 15.0 20.40 5.32 13.0 20.40 5.40 13.0 20.40 15.0 20.40 5.32 13.0 20.40 5.32 13.0 20.40 15.0 20.40 5.32 13.0 20.40 5.30 13.0 20.40 15.0 20.40 5.30 13.0 20.40 5.40 13.0 20.40 5.40 13.0 20.40 15.0 20.40	118 11.0 119.30 4.78 11.0 113.13 4.89 1.62 1.05 6.0 20.270 5.00 12.0 175.0 5.17 1.88 1.06 6.0 20.270 5.00 12.0 175.0 5.28 1.01 19.0 20.43 5.34 11.0 174.86 5.16 1.71 19.0 20.43 5.34 11.0 174.86 5.16 1.71 19.0 20.43 5.34 11.0 174.86 5.16 1.71 19.0 20.25.35 5.04 11.0 20.43 6.41 1.24 19.0 244.82 5.50 11.0 20.43 6.41 1.28 19.0 175.7 5.04 11.0 20.43 6.41 1.28 19.0 175.7 5.17 11.0 20.43 6.41 1.18 19.0 20.74 5.29 11.0 20.43 6.41 1.14 19.0 20.74 5.29 11.0 20.43 6.41 1.14 19.0 20.74 5.29 11.0 20.44 6.11 1.14 19.0 20.74 5.20 11.0 20.44 6.11 1.14 19.0 20.74 5.20 11.0 20.44 6.11 1.14 19.0 20.74 5.20 11.0 20.44 6.11 1.14 19.0 20.74 5.20 11.0 20.44 6.11 1.14 19.0 20.74 5.20 11.0 20.44 6.11 1.20 19.0 20.44 5.20 11.0 20.44 6.11 1.20 19.0 20.44 5.20 11.0 20.44 6.11 1.20 19.0 20.44 5.20 11.0 20.44 6.11 1.20 19.0 20.44 5.20 11.0 20.44 6.20 19.0 20.44 5.20 11.0 20.44 6.20 19.0 20.44 5.20 11.0 20.44 6.20 19.0 20.44 5.20 11.0 20.44 6.20 19.0 20.44 5.20 11.0 20.44 6.20 19.0 20.44 5.20 11.0 20.44 6.20 19.0 20.44 5.2		5	90.66	4.51	5.0	121.64	4.80	120	178.67	5,18	<u> </u>	2.98
6.6 6.0 28270 5.60 12.0 175.62 5.17 1.88 5.6 11.0 165.81 5.12 11.0 180.84 5.28 1.75 7.1 10.0 201.43 5.31 11.0 174.86 5.16 1.73 7.1 10.0 201.43 5.31 11.0 174.86 5.16 1.73 7.1 10.0 201.43 5.31 11.0 174.86 5.16 1.73 7.1 10.0 201.43 5.30 11.0 174.86 5.16 1.73 7.1 10.0 201.43 5.40 11.0 204.10 5.46 7.1 10.0 201.42 5.40 11.0 204.10 5.46 7.1 10.0 201.42 5.40 11.0 204.10 5.46 7.1 10.0 201.43 5.40 11.0 204.10 5.46 7.1 11.0 207.13 5.29 11.0 12.0 5.41 7.1 11.0 207.13 5.29 11.0 207.03 5.11 7.1 11.0 207.13 5.29 11.0 207.03 5.11 7.1 11.0 207.13 5.20 11.0 207.03 5.11 7.1 11.0 207.13 5.20 11.0 207.03 5.11 7.1 11.0 207.13 5.20 11.0 207.03 5.11 7.1 11.0 207.13 5.20 11.0 207.03 5.11 7.2 24.3 5.00 5.00 11.0 207.03 5.11 7.3 11.0 204.03 5.32 11.0 207.03 5.11 7.4 10.0 207.03 5.33 11.0 207.03 5.11 7.5 10.0 204.03 5.32 11.0 207.03 5.11 7.5 10.0 204.03 5.32 11.0 207.03 5.11 7.5 24.3 5.00 5.00 10.0 207.03 5.11 7.5 24.3 5.00 5.32 11.0 207.03 5.11 7.5 24.3 5.00 5.32 11.0 207.03 5.11 7.5 24.3 5.00 5.32 11.0 207.03 5.11 7.5 24.3 5.00 5.32 11.0 207.03 5.11 7.5 24.3 5.00 5.32 11.0 207.03 5.11 7.7 10.0 207.00 5.32 11.0 207.03 5.11 7.7 10.0 207.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.32 11.0 207.03 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3 5.00 5.00 5.11 7.7 24.3 5.00 5.00 5.11 7.7 24.3 5.00 5.11 7.7 24.3	6.6 6.0 28270 5.6 12.0 175.62 5.17 1.88 5.6 11.0 165.81 5.12 11.0 174.85 5.16 11.75 1.10 201.43 5.31 11.0 174.85 5.16 11.75 1.10 202.35 5.20 11.0 174.85 5.17 11.75 1.10 202.35 5.20 11.0 174.85 5.13 11.75 1.10 202.35 5.20 11.0 174.85 5.14 11.75 1.10 202.35 5.20 11.0 174.85 5.14 11.75 1.10 202.25 5.70 11.0 174.85 5.14 11.75 1.10 202.25 5.70 11.0 174.81 5.14 11.75 1.10 202.25 5.70 11.0 202.35 1 5.20 11.05 1.10 202.25 5.70 11.0 202.35 1 5.70 11.05 1.10 202.25 5.70 11.0 202.25 5.71 11.0 1.10 202.25 5.8 5.4 11.0 202.25 5.7 11.0 1.10 202.25 5.8 5.4 11.0 202.25 5.7 11.0 1.10 202.25 5.8 5.8 11.0 202.25 5.7 11.0 1.10 204.09 5.32 11.0 202.25 5.8 11.0 1.10 204.09 5.32 11.0 202.0 5.4 11.0 1.10 204.09 5.32 11.0 202.0 5.4 11.0 1.10 204.09 5.32 11.0 202.0 5.4 11.0 1.10 204.09 5.32 11.0 202.0 5.4 11.0 1.10 204.09 5.32 11.0 202.0 5.4 11.0 1.10 204.09 5.32 11.0 202.0 5.4 11.0 1.10 204.09 5.32 11.0 202.0 5.4 11.0 1.10 204.09 5.32 11.0 202.0 5.4 11.0 1.10 202.25 5.8 5.9 11.0 202.0 5.4 11.0 1.10 202.25 5.8 5.9 11.0 202.0 5.4 11.0 1.10 202.25 5.8 5.9 11.0 202.0 5.4 11.0 1.10 202.00 5.32 11.0 202.0 5.4 11.0 1.10	-	8	65.66	4.18	11.0	119.30	4.78	1.0	133,35	4.89	1.82	203
1,000 16,844 5,12 13,00 188,84 5,28 1,75 13,00 188,84 5,28 1,75 13,00 188,84 5,28 1,75 13,00 13,04 13,05 13,04 13,05 13,04 13,05 13,04 13,05 13,04 13,05 13,04 13,05 13,04 13,05 13,04 13,05 13,04 13,05 13,04 13,05	## 6.0 165.81 5.12 13.0 188.84 5.28 1.75 10.0 154.64 5.04 11.0 174.86 5.21 0.73 10.0 154.64 5.04 11.0 174.86 5.24 0.73 10.0 154.64 5.04 11.0 174.86 5.24 0.73 10.0 154.64 5.04 11.0 174.86 5.24 0.73 10.0 244.82 5.50 13.0 40.34 5.28 10.0 244.82 5.30 13.0 40.34 5.28 10.0 244.82 5.30 13.0 40.34 5.32 11.0 262.82 5.67 13.0 234.49 5.44 11.0 262.82 5.67 13.0 234.49 5.44 11.0 262.82 5.67 13.0 234.49 5.44 11.0 207.18 5.33 10.0 247.08 5.51 11.0 207.18 5.33 10.0 247.08 5.51 11.0 207.18 5.33 10.0 247.08 5.51 11.0 207.18 5.30 10.0 247.08 5.51 11.0 207.18 5.30 10.0 247.08 5.51 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 247.08 5.31 11.0 207.18 5.30 11.0 24	03	13.0	155,46	5,05	8	282,70	5.66	5.0 0.2	175.62	5.17	1.88	 3
1, 10	1, 10 154.64 5,04 14,0 143,66 5,21 0,73 1, 10, 10, 10,4,04 5,24 14,0 14,46 5,14 1,74 1, 10, 10, 10,4,04 5,24 10,0 14,746 5,14 1,74 1, 10, 10, 10,4,05 5,24 10,0 167,32 5,24 1,74 1, 10, 10, 10,4,02 5,56 14,0 20,34 6,11 1,24 1, 10, 10, 10, 10, 10, 10, 10, 10, 10,	,	80	88.45	8	6.0	168,81	5.12	13.0	196.94	5.28	1,75	2,0G
100 201.43 5.31 11.0 174.85 5.16 1.71 11.0 11.0 202.01 5.34 11.0 11.4 85 5.16 1.71 11.0 11.0 11.0 11.0 11.0 11.0 11.0	100 201.43 5.31 11.0 174.85 5.16 1.71 100 202.43 5.24 11.0 202.78 5.34 11.28 24 6.0 202.33 5.60 13.0 480.34 6.11 124 25 6.0 202.33 5.60 13.0 480.34 6.11 124 25 10.0 244.22 5.54 14.0 203.51 5.32 1.09 24.42 5.54 14.0 203.51 5.32 1.09 24.42 5.54 13.0 476.11 6.17 1.09 24.10 262.82 5.77 13.0 476.11 6.17 1.09 25 10.0 177.75 5.27 13.0 476.11 6.17 1.09 27 10.0 197.83 5.29 13.0 274.89 5.41 1.14 27 11.0 207.18 5.33 10.0 227.09 5.51 1.14 28 10.0 227.69 5.47 10.0 227.09 5.51 1.14 29 11.0 207.89 5.47 10.0 227.09 5.51 1.14 20 22.43 5.50 11.0 203.27 5.49 1.14 21 10.0 227.89 5.47 10.0 225.12 5.46 21 11.0 207.89 5.32 11.0 203.29 0.05 21 11.0 204.99 5.32 11.0 204.99 0.00 21 11.0 204.99 5.32 11.0 204.89 0.05 21 11.0 204.99 5.32 11.0 204.89 0.05 21 11.0 204.99 5.32 11.0 204.89 0.05 21 11.0 204.99 5.32 11.0 204.89 0.05 21 11.0 204.99 5.32 11.0 204.89 0.05 21 11.0 204.99 5.32 11.0 204.89 0.05 21 11.0 204.99 5.32 11.0 204.89 0.05 21 22 5.54 5.50 11.0 204.89 0.05 21 22 5.54 5.55 11.0 204.89 0.05 21 22 5.54 5.55 11.0 204.89 0.05 21 22 5.54 5.50 11.0 204.89 0.05 21 22 5.54 5.50 11.0 204.89 0.05 21 22 5.54 5.50 11.0 204.89 0.05 21 22 5.54 5.50 11.0 204.89 0.05 21 22 5.54 5.50 11.0 204.89 0.05 21 22 5.54 5.55 11.0 204.89 0.05 21	: =	14.0	212.41	5.36	÷.	154.04	20,0	1,0	183.66	5.21	6.73	98,0
101 1130 188281 5.24 10.0 208.78 5.34 1.28 1.28 1.50 208.35 5.34 1.28 1.50 208.35 5.34 1.28 1.50 208.35 5.34 1.28 1.50 208.35 5.00 1.30 400.34 6.10 204.12 5.23 1.47 1.28 1.50 208.34 6.10 204.12 5.20 1.30 400.34 1.30 1.30 1.30 1.30 1.30 1.30 1.30 1.30	101 1130 188281 5.24 10.0 208.78 5.34 1.28 1.28 1.50 208.35 5.50 13.0 187.22 5.23 1.47 1.28 1.50 208.35 5.50 13.0 187.22 5.23 1.47 1.47 1.50 208.35 1.50 208.40 5.46 2.08 1.47 1.28 1.50 208.35 1.47 1.28 1.50 208.35 1.50 208.40 5.46 1.09 2.4482 5.50 14.0 208.40 5.46 1.09 2.4482 5.50 14.0 208.35 1.50 1.28 1.09 1.75.76 5.77 14.0 175.76 5.77 14.0 175.76 5.77 14.0 175.76 5.77 14.0 175.76 5.77 14.0 175.76 5.77 14.0 175.76 5.77 14.0 175.76 5.77 14.0 175.76 5.77 14.0 175.76 1.28 1.28 1.28 1.29 1.20 1.20 1.20 1.20 1.20 1.20 1.20 1.20	: \$2	0.0	117.75	4.77	10,0	201.43	5.31	1.0	174.85	5.16	1.71	1,49
6.0 205.25 6.32 13.0 167.32 5.23 147 5.0 204.82 5.50 14.0 203.44 6.1 10.0 244.82 5.50 14.0 203.54 6.2 6.2 6.7 10.0 203.51 5.32 6.3 10.0 244.82 5.50 14.0 203.51 6.4 10.0 244.82 5.50 14.0 203.51 6.5 10.0 175.76 5.7 10.0 172.83 6.5 10.0 175.76 5.7 10.0 172.83 6.5 10.0 277.83 5.33 10.0 257.02 7.1 10.0 277.83 5.33 10.0 257.02 7.2 11.0 277.83 5.33 10.0 257.02 7.3 10.0 277.65 5.7 10.0 7.4 10.0 277.65 5.7 10.0 7.5 10.0 277.	6.6 205.25 6.32 13.0 187.32 5.23 14.7 15.6 5.9 14.7 15.0 187.32 5.23 14.7 15.0 187.32 5.23 14.7 15.0 187.32 5.23 14.7 15.0 187.32 5.23 14.7 15.0 187.32 5.24 6.11 12.4 15.0 187.32 5.54 15.3 15.3 15.3 15.3 15.3 15.3 15.3 15.3	5	0.4	149.90	50.0	13.0	180.51	5.24	10.0	208.78	£.5	2	1,39
15.0 230.93 5.60 13.0 450.34 6.11 1.24 5.0	150 150 150 150 150 150 150 150 150 150	: #	5	139.54	đ	9	205.35	6.32	13.0	187,32	5.23	1.47	7.
90 8.0 28134 5.64 10.0 22810 5.46 2.08 4.1 10.0 24452 5.50 14.0 20131 5.32 1.09 4.2 11.0 28222 5.57 13.0 27149 5.44 1.15 5.2 10.0 175.76 5.77 10.0 172.83 5.19 5.2 10.0 175.76 5.77 10.0 172.83 5.11 5.2 11.0 207.18 5.33 10.0 247.09 5.51 5.3 10.0 247.09 5.57 10.0 172.83 5.11 5.4 10.0 207.18 5.33 10.0 247.09 5.51 5.4 10.0 227.26 5.47 10.0 247.09 5.51 5.5 10.0 175.76 5.47 10.0 247.09 5.51 5.6 10.0 243.27 5.44 5.8 5.8 5.4 10.0 170.18 5.14 1.14 5.2 244.58 5.00 10.0 228.27 5.44 5.2 10.0 204.09 5.32 11.0 240.04 6.87 10.0 5.4 5 5 5 5 5 5 5 5 5 5 5 5.4 5 5 5 5 5 5 5 5 5.4 5 5 5 5 5 5 5 5.5 5 5 5 5 5 5 5 5.5 5 5 5	90 8.0 281.74 5.64 10.0 228.10 5.46 2.08 4.1 10.0 244.82 5.50 14.0 201.51 5.32 1.09 4.2 11.0 282.82 5.67 13.0 271.49 5.44 1.15 5.2 10.0 175.76 5.77 10.0 271.49 5.44 1.15 5.2 10.0 175.76 5.77 10.0 172.83 5.11 5.2 11.0 207.19 5.33 10.0 247.09 5.51 5.3 10.0 247.09 5.51 1.20 6.0 255.86 5.54 10.0 247.09 5.51 7.1 10.0 237.50 5.47 10.0 225.12 5.46 7.2 11.0 228.10 5.46 11.0 34.02 5.46 7.2 11.0 228.10 5.46 11.0 34.02 5.46 7.2 11.0 228.10 5.49 11.0 34.02 5.89 7.2 12 12 2.5 5.89 5.31 11.0 226.46 5.32 7.3 10.2 24.4.58 5.33 11.6 24.4.8 5.42 7.4 10.0 204.09 5.32 11.0 271.39 5.44 7.5 10.0 204.09 5.32 11.0 271.39 5.44 7.6 10.0 204.09 5.32 11.0 271.39 5.44 7.7 10.0 204.09 5.32 11.0 271.39 5.44 7.8 10.0 204.09 5.32 11.0 271.39 5.44 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.1 2.5 6.48 7.2 24.3 00.09 6.32 11.0 208.76 7.3 24.3 00.09 6.32 11.0 208.76 7.4 2.5 6.48 7.4 2.5 6.48 7.4 2.5 6.48 7.4 2.5 6.48 7.4 3.5 206.00 5.32 11.0 208.76 7.4 3.5 206.00 5.32 11.0 208.76 7.4 3.5 206.00 5.32 11.0 208.76 7.4 3.5 206.00 5.32 11.0 208.76 7.5 206.00 5.32 11.0 208.76 7.7 3 206.00 5.32 11.0 208.76 7.8 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.9 206.00 5.32 11.0 208.76 7.0 206.00 5.32 11.0 208.76 7.0 206.00 5.32 11.0 208.76 7.0 206.00 5.32 11.0 208.76 7.0 208.70	<u> </u>	18.0	268.48	5.59	15.0	330.83	5.80	13.0	450.34	6.11	1.24	1.69
A1 [0.0) 244.82 5.50 [4.0) 203.51 5.32 1.09 (54 6.0 262.25 5.73 13.0 478.11 6.17 1.09 (4.3) 11.0 262.25 5.73 13.0 478.11 6.17 1.09 (1.0) 17.2 13.0 271.49 27.4 1.26 1.26 (1.0) 17.0 17.0 27.14 27.1 1.20 1.26 (1.0) 27.16 5.33 10.0 27.02 5.71 1.26 (1.1) 20.7 5.33 10.0 27.02 5.71 1.26 (1.1) 20.7 5.33 10.0 25.02 6.22 1.26 (1.1) 20.7 5.7 10.0 22.13 5.5 1.14 (2.1) 10.0 25.12 1.00 170.18 5.4 1.14 (2.2) 20.0 25.2 1.10 27.03 5.4 1.20 (2.2) 20.0	41 10.0 244.82 5.50 14.0 203.51 5.32 1.09 6.4 6.0 262.5 5.77 13.0 478.11 6.17 1.09 6.4 10.0 175.76 5.17 13.0 478.11 6.17 1.09 6.10 175.76 5.17 10.0 472.83 5.16 1.26 6.10 17.0 197.83 5.23 10.0 27.08 5.51 6.10 17.0 27.18 5.33 10.0 27.08 6.22 1.26 6.11 10.0 277.89 5.33 10.0 27.08 6.22 1.26 6.12 10.0 255.86 5.77 10.0 275.12 5.77 1.09 6.13 10.0 255.86 5.77 10.0 275.12 5.77 6.14 10.0 225.80 5.77 10.0 225.12 5.89 6.15 11.0 275.90 5.32 11.0 275.90 6.17 11.0 244.89 5.32 11.0 275.90 6.17 11.0 204.09 5.32 11.0 208.78 5.77 6.10 10.0 204.09 5.32 11.0 208.78 5.34 6.11 10.0 204.09 5.32 11.0 208.78 5.34 6.12 10.0 204.09 5.32 11.0 208.78 5.34 6.13 11.0 208.78 5.34 6.14 11.0 204.09 5.32 11.0 208.78 5.34 6.15 11.0 208.78 5.34 6.17 10.0 204.09 5.32 11.0 208.78 5.34 6.18 11.0 208.78 5.34 6.19 206.00 5.32 11.0 208.78 5.34 6.10 204.09 5.32 11.0 208.78 5.34 6.10 204.09 5.32 11.0 208.78 5.34 6.10 204.09 5.32 11.0 208.78 5.34 6.10 204.09 5.32 11.0 208.78 5.34 6.10 204.09 5.32 11.0 208.78 6.34 6.10 204.09 6.32 11.0 208.78 6.34 6.10 204.09 6.32 11.0 208.78 6.34 6.10 204.09 6.32 11.0 208.78 6.34 6.10 204.09 6.32 11.0 208.78 6.34 6.10 204.09 6.32 11.0 208.78 6.34 6.10 204.09 6.32 11.0 208.78 6.34 6.10 204.09 6.32 11.0 208.78 6.34 6.10 204.09 6.32 11.0 208.78 6.34 6.10 204.09 6.32 11.0 208.78 6.34 6.10 204.09 6.32 11.0 208.78 6.34 6.10 204.09 6.32 11.0 208.78 6.34 6.10 204.09 6.32 11.0 208.78 6.34 6.10 208.7	9	13.0	134.55	9	0.6	281.74	5.62	0,0	236.10	5.46	5.03	1,75
(54) 8.0 308.25 6.73 13.0 478.11 6.17 1.09 4.4 1.10 268.28 6.67 13.0 23.14 9.54 1.15 2.2 10.0 127.63 5.29 13.0 201.72 5.71 1.28 2.1 11.0 207.18 5.35 10.0 247.63 5.51 1.14 2.1 11.0 207.18 5.35 10.0 207.22 5.57 1.14 2.1 10.0 207.22 5.77 1.04 207.22 1.14 2.1 10.0 207.22 5.77 1.04 1.14 1.14 2.1 10.0 207.13 5.67 1.14 1	13.0 13.0	-	12.0	224.65	5.41	00	244.82	5.50	4.0	203,51	5.32	1,09	0.91
11.0 282.82 5.57 13.0 221.49 5.44 1.15 11.0 176.75 5.77 10.0 172.83 5.16 12.0 175.75 5.77 10.0 172.83 5.17 12.0 17.0 17.0 207.18 5.23 10.0 247.06 5.51 1.14 17.0 207.18 5.23 10.0 247.06 5.51 1.14 17.1 8.0 322.65 5.47 10.0 283.27 5.57 1.14 17.1 8.0 322.65 5.47 10.0 283.27 5.57 1.14 17.1 8.0 322.65 5.47 10.0 283.27 5.46 17.1 10.0 237.80 5.47 10.0 283.27 5.46 17.1 10.0 238.10 5.48 11.0 34.04 4.87 1.10 18.0 204.09 5.32 11.0 281.89 0.35 1.10 17.1 10.2 215.33 5.33 11.6 281.89 0.35 1.10 17.2 24.3 30.09 5.32 11.0 281.89 0.35 1.20 17.1 10.2 205.00 5.32 11.0 281.89 0.35 1.20 17.1 10.0 204.09 5.32 11.0 281.89 0.35 1.20 17.1 10.0 204.09 5.32 11.0 281.89 0.35 1.30 17.1 10.0 204.09 5.32 11.0 281.89 0.35 1.30 17.1 10.0 204.09 5.32 11.0 281.89 0.35 1.30 17.1 10.0 204.09 5.32 11.0 281.89 0.35 1.30 17.1 10.0 204.09 5.32 11.0 281.89 0.35 1.30 17.1 10.0 204.09 5.32 11.0 281.89 0.35 1.30 17.1 10.0 204.09 5.32 11.0 281.89 0.35 1.30 17.1 10.0 204.09 5.32 11.0 281.89 0.35 1.30 17.1 17.1 281.80 0.40 0.40 0.40 0.40 0.40 0.40 0.40 17.1 17.1 17.1 17.1 17.1 17.1 17.1 17.1	11.0 262.82 5.57 13.0 221.49 5.44 1.15 32. 13.0 177.57 5.77 10.0 172.83 5.16 23. 13.0 217.78 5.23 10.0 247.09 5.51 24. 13.0 207.18 5.23 10.0 247.09 5.51 25. 14.0 207.18 5.23 10.0 247.09 5.51 26. 10.0 340.21 5.83 10.0 247.09 5.57 27. 14.0 207.25 5.47 10.0 232.27 5.57 28. 10.0 237.50 5.47 10.0 232.27 5.57 28. 10.0 237.50 5.47 10.0 232.27 5.57 29. 10.0 237.50 5.47 10.0 232.27 5.57 29. 10.0 237.50 5.47 10.0 232.27 5.49 20. 10.0 24.58 5.50 10.0 235.2 5.46 20. 24.4.58 5.50 10.0 236.84 5.35 20. 24.4.58 5.30 11.0 24.0.9 5.44 20. 24.4.58 5.30 11.0 24.0.9 5.44 21. 10.2 215.53 5.33 11.6 24.4.8 5.42 22. 54.8.8 0.31 11.6 24.4.8 5.42 23. 24.3 0.09 5.32 11.0 20.8.76 24.3 0.09 5.32 11.0 20.8.76 25. 64.89 5.32 11.0 20.8.76 26. 10.0 20.4.09 5.32 11.0 20.8.76 27. 10.0 20.4.09 5.32 11.0 20.8.76 28. 10.0 20.4.09 5.32 11.0 20.8.76 29. 20.0.09 5.32 11.0 20.8.76 20. 20.0.09 5.32 11.0 20.8.76 20. 20.0.09 5.32 11.0 20.8.76 20. 20.0.09 5.32 11.0 20.8.76 20. 20.0.09 5.32 11.0 20.8.76 21. 20.0.09 5.32 11.0 20.8.76 22. 22. 24.3 0.09 5.32 11.0 20.8.76 23. 24.3 0.09 5.32 11.0 20.8.76 24.3 0.09 5.32 11.0 20.8.76 25. 64.80 5.32 11.0 20.8.76 26. 20.00 5.32 11.0 20.8.76 27. 27. 27. 27. 27. 27. 27. 27. 27. 27.	<u>=</u>	14.0	261.88	19.55	0,8	308.25	5,73	13.0	478,11	6.17	1.09	2:
120 175.76 6.17 10.0 173.83 6.16 128 128 170 170 170 170 170 170 170 170 170 170	21 10.0 175.76 5.17 10.0 173.83 5.16 128 128 1.10 175.75 5.17 10.0 177.85 5.17 12.0 12.0 17.0 17.0 17.0 17.0 17.0 17.0 17.0 17	2	15.0	227.89	5,43	11,0	262,82	5,57	13,0	231.49	5. ‡	1,15	1,02
1.0	1,0 197,63 5.29 13.0 301,72 5.71 1.20	20	7	137.51	4.82	10.0	175.76	5.17	10.0	173.83	5.16	1.28	1.26
21 11.0 207.18 5.33 10.0 287.08 5.51 1.14 10.0 232.26 5.78 10.0 500.82 6.22 1.26 11.1 8.0 237.26 5.47 10.0 232.27 5.57 1.94 12.1 10.0 237.60 5.47 10.0 232.27 5.57 1.94 12.1 10.0 237.60 5.47 10.0 235.12 5.46 1.14 12.2 24.4.5 5.08 11.0 324.02 5.85 1.16 12.1 10.0 244.8 5.08 12.0 129.94 4.87 0.75 12.1 10.2 244.8 5.50 10.0 336.44 5.82 1.01 12.2 24.3 30.09 5.32 11.0 231.33 5.44 0.67 12.3 24.3 30.09 5.33 11.4 208.38 5.34 1.20 12.3 24.3 30.09 5.33 11.4 208.78 5.34 1.20 13.3 24.3 30.09 5.32 11.0 208.78 5.34 1.20 13.4 3.9 208.00 5.32 11.0 208.78 5.34 1.20 13.5 24.3 30.09 5.32 11.0 208.78 5.34 1.20 13.5 24.3 30.09 5.32 11.0 208.78 1.34 1.35 13.5 24.3 30.09 5.32 11.0 208.78 1.34 1.35 13.5 24.3 30.09 5.32 11.0 208.78 1.34 1.35 13.5 24.3 30.09 5.32 11.0 208.78 1.34 1.35 13.5 24.3 30.09 5.32 11.0 208.78 1.34 1.35 13.5 24.3 30.09 5.32 11.0 208.78 1.34 1.35 13.5 24.3 30.09 5.32 11.0 208.78 1.34 1.35 13.5 24.3 30.09 5.32 11.0 208.78 1.34 1.35 13.5 24.3 30.09 5.32 11.0 208.78 1.34 1.35 13.5 24.3 30.09 5.32 11.0 208.78 1.35	21 11.0 207.18 5.33 10.0 287.08 5.51 1.14 10.0 322.66 5.78 10.0 500.82 6.22 1.26 13.0 10.0 227.60 5.47 10.0 232.27 5.57 1.94 10.0 227.60 5.47 10.0 225.12 5.46 11.0 238.10 5.64 10.0 170.18 5.14 1.157 11.0 160.73 5.04 12.0 170.18 5.14 1.157 12.0 244.58 5.50 10.0 236.94 5.85 1.08 12.1 10.2 215.53 5.33 11.6 224.38 5.42 0.07 12.1 10.2 215.53 5.33 11.6 224.38 5.42 0.07 12.1 10.2 215.53 5.33 11.6 224.38 5.42 0.05 11.1 10.2 206.00 5.32 11.0 208.76 5.34 1.29 11.1 10.3 206.00 5.32 11.0 208.76 5.34 1.20 12.1 10.3 204.08 5.32 11.0 208.76 5.34 1.20 12.1 10.3 204.08 5.32 11.0 208.76 5.34 1.23 12.1 10.3 206.00 5.32 11.0 208.76 5.34 1.23 13.1 10.3 206.00 5.32 11.0 208.76 1.33 14.1 4.3 206.00 5.32 11.0 208.76 1.33 14.1 4.3 206.00 5.32 11.0 208.76 1.33 14.1 4.3 206.00 5.32 11.0 208.76 1.33 14.1 4.3 206.00 5.32 11.0 208.76 1.33 14.1 4.3 206.00 5.32 11.0 208.76 1.33	7	13.0	164.75	5,10	13.0	197,63	5.29	13.0	301.72	5,71	22	3.
(50 10.0 340.21 5.83 10.0 560.82 6.22 1.26 (51 10.0 237.56 5.77 10.0 283.27 5.57 1.94 (52 10.0 237.56 5.54 10.0 255.12 5.46 1.14 (53 11.0 237.56 5.54 10.0 170.18 5.14 1.57 (53 11.0 238.10 5.46 11.0 334.02 5.85 1.08 (54 12.0 12.84 4.87 0.75 (55 12.0 244.58 5.50 10.0 336.64 5.32 1.08 (57 10.2 244.58 5.33 11.6 242.46 5.32 1.05 (57 10.2 244.58 5.33 11.6 242.46 5.32 1.05 (57 10.2 245.53 5.33 11.6 242.46 5.32 1.05 (57 10.3 204.09 5.32 11.0 208.76 5.34 1.29 (57 10.3 204.09 5.32 11.0 208.76 5.34 1.29 (57 10.3 204.09 5.32 11.0 208.76 5.34 1.20 (57 10.3 204.09 5.32 11.0 208.76 5.34 1.20 (57 10.0 204.09 5.32 11.0 208.76 5.34 1.23 (57 10.0 204.09 5.32 11.0 208.76 1.33 (57 10.0 204.09 5.32 11.0 208.76 1.34 (57 10.0 204.09 2.34 (57 10.0 204.09 2.34 (57 10.0 204.09 2.34 (57 10.0 204	(50 10.0 340.21 5.83 10.0 560.82 6.22 1.26 (51 10.0 255.65 5.74 10.0 285.12 5.57 1.94 (52 10.0 255.65 5.54 10.0 170.18 5.14 1.57 (53 11.0 255.65 5.54 10.0 170.18 5.14 1.57 (53 11.0 255.10 5.46 11.0 394.02 5.85 (54 12.0 244.58 5.50 10.0 336.94 5.85 (57 16.0 244.58 5.50 10.0 336.94 5.82 (57 16.0 244.58 5.33 11.6 24.38 5.34 (57 16.0 244.58 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.32 11.0 24.48 5.42 (57 16.0 24.48 5.32 11.0 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.33 11.6 24.48 5.42 (57 16.0 24.48 5.42 11.0 24.48 5.42 (57 16.0 24.48 5.42 11.0 24.48 5.42 (57 16.0 24.48 5.42 11.0 24.48 5.42 (57 16.0 24.48 5.42 11.0 24.48 5.42 (57 16.0 24.48 5.42 11.0 24.48 5.42 (57 16.0 24.48 5.42 11.0 24.48 5.42 (57 16.0 24.48 5.42 11.0 24.48 5.42 (57 16.0 24.48 5.42 11.0 24.48 5.42 (57 16	77	16.0	182.52	521	11,0	207,19	5,33	10.0	247.08	5.51	1.34	1.35
1,11 8.0 322.65 6.78 10.0 283.27 5.57 1.94 10,0 255.86 5.47 10,0 255.12 5.46 11,0 255.86 5.47 10,0 255.12 5.46 11,0 255.86 5.47 10,0 170.18 11,0 160.73 5.08 12,0 129.54 4.87 0.75 12,0 244.58 5.50 11,0 236.54 5.82 1.04 17,2 16.0 204.09 5.32 11,0 236.54 5.82 1.04 17,2 16.2 24.83 0.31 11,6 242.46 5.42 1.29 17,2 2.5 64.83 0.31 11,6 242.46 5.42 1.29 17,0 2.65.09 5.53 14.1 204.78 5.34 1.20 17,0 2.5 64.83 0.31 1.6 242.8 5.44 1.20 17,0 2.5 64.83 0.31 1.6 242.8 5.44 1.20 17,0 2.5 64.83 0.31 1.6 242.8 5.44 1.20 17,0 2.5 64.83 0.31 1.6 242.8 5.44 1.20 17,0 2.5 64.83 0.31 1.6 242.8 5.44 1.20 17,0 2.5 64.83 0.31 1.6 242.8 5.44 1.20 17,0 2.5 64.83 0.31 1.6 242.8 5.44 1.20 17,0 2.5 64.83 0.31 1.6 242.8 5.44 1.20 17,0 2.5 64.83 0.31 1.6 242.8 5.44 1.20 17,0 2.5 64.83 0.31 1.6 242.8 5.44 1.20 17,0 2.5 64.83 0.31 1.6 242.8 5.44 1.20 17,0 2.5 64.83 0.31 1.6 242.8 5.44 1.20 17,0 2.5 64.83 0.31 1.4 1.23 17,1 3.5 24.3 5.20 1.0 5.32 1.1.0 248.8 5.44 1.20 17,1 3.5 24.3 5.20 1.0 5.32 1.1.0 248.8 5.44 1.20 17,1 3.5 24.3 5.20 1.1.0 5.44 1.20 17,1 3.5 24.3 5.44 1.1.0 248.8 5.44 1.20 17,1 3.5 24.3 5.44 1.1.0 248.8 5.44 1.20 17,1 3.5 24.3 5.44 1.1.0 248.8 5.44 1.20 17,1 3.5 24.3 5.44 1.1.0 248.8 5.44 1.20 17,1 3.5 24.3 5.44 1.1.0 248.8 5.44 1.20 17,1 3.5 24.3 5.44 1.1.0 248.8 5.44 1.20 17,1 3.5 24.3 5.44 1.1.0 248.8 5.44 1.20 17,1 3.5 24.3 5.44 1.1.0 248.8 5.44 1.20 17,1 3.5 24.3 5.44 1.1.0 248.8 5.44 1.20 17,1 3.5 24.3 5.44 1.1.0 248.8 5.44 1.1.0 248.8 5.44 1.20 17,1 3.5 24.3 5.44 1.1.0 248.8 1.1.0 248.8 5.44 1.1.0 248.8 5.44 1.1.0 248.8 5.44 1.1.0 248.8 2	1,11 8.0 32,255 6.78 10.0 283,27 5.57 1.94 10.0 255,86 5.47 10.0 225,12 5.46 11.0 225,86 5.47 10.0 125,12 5.46 11.0 225,86 5.47 10.0 125,12 5.46 11.0 228,10 5.46 11.0 394,02 5.89 11.0 228,10 5.46 11.0 394,02 5.89 11.0 224,18 5.50 10.0 396,46 5.82 11.0 244,18 5.30 11.0 396,46 5.82 11.0 244,18 5.30 11.0 396,46 5.82 11.0 24,18 5.31 11.6 242,46 5.42 11.0 224,3 30.09 5.83 14.1 40.82 6.38 11.0 224,3 30.09 5.83 14.1 40.82 6.38 11.0 224,3 30.09 5.83 14.1 40.82 6.38 11.0 224,3 30.09 5.32 11.0 28,76 5.34 12.0 10.0 204,09 5.32 11.0 28,76 5.32 11.0 28,76 5.34 12.0 10.0 204,09 5.32 11.0 24,70 5.32 11.0 24,70 5.32 11.0 24,70 5.32 11.0 24,70 5.32 11.0 24,70 5.32 11.0 24,70 5.32 11.0 24,70 5.32 11.0 24,70 5.32 11.0 24,70 5	R	18.0	269.97	20.50	10.0	340.21	5.83	10.0	500.82	22.9	126	-
(34) 10.0 237.89 5.47 10.0 225.72 5.46 1.14 (198	(34) 10.0 237.89 5.47 10.0 225.12 5.46 1.14 (198	K	10.0	168.05	8.4	8.0	322.65	5.78	10.0	283.27	5.57	Ž.	1.59
(10) 6.0 255.86 5.54 10.0 170.18 5.14 1.57 (13) 11.0 228.10 5.46 11.0 394.02 5.85 1.08 (13) 12.0 224.58 5.50 10.0 12.0 120.02 (14) 12.0 244.58 5.50 10.0 120.64 5.82 1.01 (17) 10.0 204.09 5.32 11.0 221.33 5.44 0.67 (17) 10.0 204.09 5.32 11.0 221.33 5.44 0.67 (17) 10.0 204.09 5.32 11.0 221.88 0.36 0.36 (17) 10.0 204.09 5.32 11.0 208.76 5.34 1.29 (18) 10.0 204.09 5.32 11.0 208.76 5.34 1.20 (19) 204.09 5.32 11.0 208.76 5.34 1.23 (11) 9.9 206.00 5.32 11.0 208.76 5.34 1.23 (12) 22	1.09 8.0 255.86 5.54 10.0 170.18 5.14 1.57 1.00 224.56 11.0 334.02 5.85 1.08 1.30 11.0 228.10 5.45 11.0 334.02 5.85 1.08 1.31 12.0 244.58 5.50 10.0 336.64 5.82 1.08 1.32 10.0 204.09 5.32 11.0 231.33 5.44 0.07 1.32 10.2 215.53 5.33 11.6 242.46 5.42 0.07 1.32 24.3 0.09 5.32 11.0 208.76 5.34 0.00 1.37 24.3 0.09 5.32 11.0 208.76 5.34 1.29 1.10 10.0 204.09 5.32 11.0 208.76 5.34 1.20 1.11 9.9 206.00 5.32 11.0 208.76 5.34 1.23 1.12 22.6 33 5.41 1.3 226.83 5.41 1.33 1.13 22.6 33 5.41 1.3 226.83 5.41 1.33 1.14 3.9 206.00 5.32 11.4 226.83 5.41 1.33 1.35 Avg of Individual Ration 1.41	8	13.0	208.19	5.34	10.0	237,50	5.47	10,0	235.12	5.46	1.14	1.13
139 11.0 238.10 6.46 11.0 334.02 5.85 1.08 1.08 1.37 15.0 180.73 5.08 12.0 180.84 4.87 0.75 17.0 180.73 5.08 12.0 180.84 4.87 0.75 17.0 180.73 5.09 11.0 334.02 5.85 1.00 1.75 17.0 12.0 204.09 5.32 11.0 231.33 5.44 0.67 1.01 1.01 1.02 24.3 10.09 5.32 11.0 231.33 5.44 0.67 1.29 1.37 2.4 30.09 5.32 11.0 24.08 5.42 0.36 0.40 1.00 10.0 204.09 5.32 11.0 202.76 5.34 1.20 1.00 10.0 204.09 5.32 11.5 226.83 5.41 1.38 1.38 1.38 1.38 1.38 1.38 1.38 1.3	130 11.0 238.10 E.48 11.0 394.02 5.85 1.08 1.08 1.09 1.09 1.00 1.00 1.00 1.00 1.00 1.00		10.0	162.47	80.8	09	255.85	15.00	10,0	170.18	5,14	1.57	1.05
137 1130 160,73 5.08 12.0 128.94 4.87 0.75 14.9 12.0 244,58 5.50 10.0 336,45 5.92 1.01 17.7 16.0 264,68 5.50 11.0 231,33 5.44 0.67 17.1 10.2 215,53 5.33 11.6 24.48 5.42 1.29 17.1 2.5 64,85 0.31 1.6 28.86 5.42 1.29 17.1 10.2 204,08 5.63 14.1 40,82 6.58 3.40 17.1 10.2 204,08 5.32 11.0 208,76 5.34 1.20 17.1 10.2 204,08 5.32 11.0 208,76 5.34 1.20 17.1 10.2 204,08 5.32 11.0 208,76 5.34 1.23 17.1 10.2 204,08 5.32 11.0 208,76 1.30 17.2 2.3 8.40 07 Means 1.38 1.38 2.3 Avg of Individual Ration 1.41	120 160.73 5.08 12.0 128.94 4.87 0.75 120 244.58 5.50 10.0 236.64 5.32 1.01 121 10.2 244.58 5.50 11.0 231.33 5.44 0.67 121 10.2 244.58 5.33 11.6 242.68 5.42 1.01 122 24.3 30.09 5.33 14.1 40.82 6.58 0.40 123 24.3 30.09 5.32 11.0 248.78 5.34 1.20 120 10.0 204.08 5.32 11.0 248.78 5.34 1.20 121 9.9 206.00 5.32 11.0 228.78 5.41 1.23 122	28	13.0	218.59	5.39	11.0	238.10	5,48	11.0	384.02	5.85	1.08	1.78
120 244.56 5.50 10.0 336.64 5.82 1.01 172 16.0 204.09 5.32 11.0 231.33 5.44 0.67 173 16.0 204.09 5.32 11.0 231.33 5.44 0.67 174 16.0 204.09 5.32 11.0 24.28 5.42 1.29 175 16.0 204.09 5.32 11.0 208.76 5.34 1.20 176 19.9 208.00 5.32 11.0 208.76 5.34 1.20 177 19.9 208.00 5.32 11.0 208.76 5.34 1.20 178 22 22 Ratio of Means 1.38 23 Avg of Individual Ration 1.41	120 244.56 5.50 10.0 336.64 5.82 1.01 172 16.0 204.09 5.32 11.0 231.33 5.44 0.67 173 16.0 204.09 5.32 11.0 231.33 5.44 0.67 174 24.3 50.3 11.6 242.46 5.42 1.29 175 24.3 50.0 5.3 11.0 208.76 5.34 1.29 170 10.0 204.09 5.32 11.0 208.76 5.34 1.20 171 9.9 206.00 5.32 11.0 208.76 5.34 1.23 171 9.9 206.00 5.32 11.0 208.76 5.34 1.23 172 24.3 Subsort Geometra 1.35 23 Avg of Individual Ration 1.41	R	13.0	215.15	5.37	13.0	160,73	5,08	42.0	129.94	4.87	0.75	0.80
1,72 16.0 204.09 5.32 11.0 221.33 5.44 0.67 1.20 1.3 1.4 2.5 64.88 0.31 1.6 88.88 0.35 0.40 0.40 0.40 0.40 0.40 0.40 0.40 0.4	1,72 16.0 204.09 5.32 11.0 221.33 5.44 0.67 1,12 10.2 215.53 5.33 11.6 242.48 5.42 1.29 1,2 2.5 64.83 0.31 1.6 242.48 5.32 1.29 1,2 2.43 30.09 5.32 14.1 208.78 5.34 1.20 1,1 9,9 206.00 5.32 11.0 208.78 5.34 1.23 1,1 9,9 206.00 6.32 11.0 208.78 5.34 1.23 1,1 9,9 206.00 6.32 11.0 208.78 1.35 1,2 2.3 Ratio of Means 1.35 2.3 Avg of Individual Ratios 1.41 2.9 FIG. 9B	8	40	242.88	5,49	120	244.58	5,50	10.0	338,64	5.82		1.39
1,12 10.2 215.53 5.33 11.6 242.48 5.42 1.29 1,17 2.5 64.83 0.31 1.6 98.38 0.36 0.40 1,18 24.3 30.09 5.53 14.1 40.82 6.58 3.44 1.20 1,10 204.09 5.32 11.5 226.83 6.41 1.20 1,11 9,9 206.00 5.32 11.5 226.83 6.41 1.23 1,23 Ratio of Means 1.38 2,3 Ratio of Means 1.38 2,3 Avg of Individual Ratios 1.41	1.2 10.2 215.53 5.33 11.6 242.48 5.42 1.29 1.37 2.5 64.83 0.31 1.6 98.38 0.36 0.40 1.32 24.3 30.09 5.83 14.1 40.82 8.58 3.54 1.20 1.0. 204.09 5.32 11.0 208.76 5.34 1.20 1.1 9.9 208.00 5.32 11.5 228.83 5.41 1.23 2.1 Ratio of Means 1.38 2.2 Avg of Individual Ratios 1.41 2.3 Avg of Individual Ratios 1.41	R	12.0	303,43	5,72	16.0	204.09	5,32	11.0	27.33	5,4 1	0.67	0.76
1.37 2.5 6.48 0.31 1.6 98.38 0.36 0.40 1.32 2.4.3 30.09 5.83 14.1 40.82 8.58 3.54 1.20 1.00 204.09 5.32 11.5 228.83 6.41 1.20 1.10 9.9 206.00 5.32 11.5 228.83 6.41 1.23 1.24 1.25 1.25 1.25 1.25 1.25 1.25 1.25 1.25	1.37 2.5 6.438 0.31 1.6 98.38 0.36 0.40 1.32 2.4.3 30.09 5.83 14.1 40.82 8.58 30.39 1.00 204.09 5.32 14.5 228.83 6.41 1.20 1.11 9.9 208.00 5.32 11.5 228.83 6.41 1.23 1.12 2.4 30.09 5.32 11.5 228.83 6.41 1.23 1.23 Ratio of Means 1.38 1.39 Arg of Individual Ratios 1.41	100	9 (*****	;	40.0	248.83		44.8	242.48	5.42	1.29	141
22 24.3 30.09 5.83 14.1 40.82 6.58 30.89 30.89 (10.0 204.08 5.34 1.20 1.20 1.00 204.08 5.34 1.20 1.20 1.20 1.20 1.20 1.20 1.20 1.20	22 24.3 30.09 5.83 14.1 40.82 6.58 30.89 30.89 30.90 3.20 10.0 204.09 5.32 11.0 208.76 5.34 1.20 1.20 10.0 204.09 5.32 11.0 208.76 5.34 1.20 1.20 206.00 5.32 11.0 208.76 5.34 1.23 1.23 1.23 Ratio of Means 1.38 1.36 2.33 Avg of Individual Ratios 1.41			20 50		1 e	F4.88	1.0		98.98	0.36	976	670
.10 10.0 204.08 5.32 11.0 208.76 5.34 1.20 .11 9.9 206.00 5.32 11.5 226.83 5.41 1.23 Night/Morning Patio 2.1 Ratio of Mesns 1.38 .23 Avg of Individual Ration 1.41	10.0 204.09 5.32 11.0 208.76 5.34 1.20 11.1 9.9 206.00 5.32 11.4 228.83 5.41 1.23 Night/Morning Ratio 2.1 Ratio of Means 1.35 Avg of Individual Ratios 1.41 Fig. 9B	3 6	į	2 2	1	7,7	30.02	6.83	7	40.82	8,58	30,69	27.63
11 9,9 206.00 5,32 11.5 226.83 5.41 1.23 Night/Morning Ratio Ratio of Means 1.36 21 Ratio of Means 1.35 Avg of Individual Ratios 1.41	111 9,9 206.00 5,32 11.5 226.83 5.41 1.23 Night/Morning Ratio Ratio of Means 23 Ratio of Means Ang of Individual Ratios 1,41 Fig. 9B	2	2 5	164.78	2.50	10.01	204.09	5.32	1.0	208.76	3,74	120	1.38
Night/Morning Ratio Ratio of Means Ratio of Geo Means Avg of Individual Ratios	Night/Morning Ratio Ratio of Means As Ratio of Means Ang of Individual Ratios	Jed Mean	2	167.47	5,1	6,0	206.00	5,32	#	226,83	5,41	1.23	1.15
Ratio of Means 23 Avg of Individual Ratios	Ratio of Means And of Individual Ratios Fig. 9B	Fed/Fastlm	7 Patio (M	oculus Do	sing}				Night/Mou	ming Ratio			
121 Ratio of Means 123 Avg of Individual Ratios	121 Ratio of Means 123 Avg of Individual Ratios Fig. 9B				•								
1.29 Avg of Individual Ratios	Avg of Individual Ration Fig. 9B	Carbo of Me	ans.		121				Ratio of h	desns Neo Meana		<u>1</u> 1	
	Fig. 9B	Avg of Indi	viduai Rat	50	129				Avg of In	dividual Ra	HOR	1.41	
	Fig. 9B							!					

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		93.35 93.00 95.73	16.07%		
(N=30)	osule Intact Cmax	Ratio of Means % Ratio of Geo Means % Avg of Individual Ratios %	Juta-CV	Mean 13.7 hours 13.5 hours	Fig. 10A
PK Summary (N=30) Dilitazem PK	on Applesauce / Capsule Intact	94.16 93.98 96.03	88%-99% 13.47%	on Applesauce	
	Open Capsule Sprinkled on AUC:	Ratio of Means % Ratio of Geo Means % Avg of Individual Ratios %	90% C.I. Intra-CV	Tmax Open Capsule Sprinkled on Capsules Intact	

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Dilibatem AUCt Results

Formulation According to Embodiment of Invention

	Open Capsules Sprin	nkied on Applesauce (A)	Cansul	e Intact (B)	(A:B)
Subject	AUCI	Log Cmax	AUCL	Log Cmax	Ratio
1	3937.18	8.28	3251.62	8.09	1.21
2	3792.89	8.24	5502.18	8.61	0.69
3	1616.35	7.39	2358.22	7. 7 7	0.69
4	8209,44	9.01	7954.29	8.98	1.03
5	2171.26	7.68	2452.78	7.80	0.89
6	5710.90	8.65	7082.30	8.87	0.81
7	1983.56	7.59	2624.03	7.87	0.76
8	3862.46	8.26	3114.53	8.04	1.24
8	6069,65	8.71	4585.60	8.43	1.32
10	3907.33	8.27	6393.14	8.76	0.61
11	3842,58	8.25	4292.30	8.36	0.90
12	4873.82	8.49	6493.87	8.78	0.75
13	2707.85	7.90	3922.9D	8.27	0.69
14	2553.27	7.85	2159.88	7.68	1.18
15	2042,47	7.62	2902.70	7.97	0.70
16	4650.14	8.44	4769.32	8.47	0.78
17	3705.72	8.22	3454.89	8.15	1.07
19	7881.69	8.97	- 6851.45	8.83	1.15
21	6151.00	8.72	6292,65	8.75	0.98
22	2138.64	7.67	1933.52	7.57	1.11
23	3983.50	8.29	5177.74	8.55	0.77
24	3939.51	8.28	3517.56	8.17	1.12
25	2318.36	7.75	2016.26	7.61	1.12
27	2061.09	7.63	1928.02	7.56	1.15
28	2871.31	7.98	3312.87	8.11	0.87
29	4305.14	8,37	3559.57	8.18	1.21
30	3190.17	8.07	3565.88	8.18	0.89
31	3422.16	8.14	3012.17	8.01	1.14
33	4906.47	8.50	5206.52	8.56	0.94
34	2969.19	8.00	3255.28	8.09	0.91
			••••		V.3 (
Mean	3859.17	8.17	4098.47	8.24	0.96
SD	1664.90	0.42	1708.24	0.41	0.20
CV	43.14	5.10	41.68	5.03	20.69
Median	3817.74	8.25	3538.57	8.17	0.96
Geo Mean	3546.16	8.16	3773.43	6.23	0.94
Test/Ref R	atio				
Ratio of Mo	eans %	94.16			
Ratio of Go	o Means %	93.98			
	ividual Ratios	0.96			
90% C.I.		88%-99%			
Intra-CV		13.47%			

Fig. 10B

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Dillizem Cmax Results

Formulation According to Embodiment of Invention

	Open Capsule	Sprinkled o	n Applesauce (A)	Ca	psule Intaci		(A:B)
Subject	Tmax	Cmax	Log Cmax	Tmax	Cmax	Log Cmax	Ratio
Í	13.0	184,35	5.22	13.0	228.99	5.43	0.81
2	14.0	192.44	5.26	12.0	286.72	5.66	0.67
3	13.0	103.87	4.64	12.0	127.07	4.84	0.82
4	10.0	372.93	5.92	B.O	298.05	5.70	1.25
5	14.0	107.71	4.68	16.0	147.84	5.00	0.73
5 6 7	13.0	244.87	5,50	15.0	315.48	5.75	0.78
7	14.0	115.23	4.75	16.0	135.27	4.91	0.85
8	13.0	257.26	5.55	15.0	179.11	5.19	1.44
9	8.0	232.12	5.45	10.0	194.37	5.27	1.19
10	16.0	172.20	5.15	15.0	281.81	5.64	0.61
11	13.0	177.41	5,18	8.0	181.17	5.20	0.98
12	13.0	225.55	5.42	10.0	327.23	5.79	0.69
13	15.0	135.86	4.91	15.0	213.37	5.36	0.64
14	15.0	154.65	5.04	14.0	135.94	4.91	1.14
15	12.0	114.81	4.74	15.0	181.80	5.20	0.63
16	15.0	294.21	5.68	13.0	296.58	5.69	0.99
17	15.0	187.32	5.23	15.0	183.62	5.21	1.02
19	16.0	385.36	5.95	15.0	376.57	5.93	1.02
21	15.0	318.06	5,76	10.0	276.15	5.62	1.15
22	14.0	114.40	4.74	14.0	97.24	4.58	1.18
23	12.0	260.20	5.56	12.0	346.74	5.85	0.75
24	14.D	211.61	5.35	16.0	202.88	5.31	1.04
25	14.0	155.98	5.05	15.0	125.66	4.83	1.24
27	16.0	79.66	4.38	16.0	67.35	4.21	1.18
28	16.0	124.76	4.83	16.0	165.01	5.11	0.76
29	15.0	225.58	5.42	10.0	164.02	5.10	1.38
30	14.0	166,54	5.12	15.0	165.41	5.11	1.01
31	15.0	134.14	4.90	14.0	135.19	4.91	0.99
33	13.D	282.10	5.64	16.0	275.33	5.62	1.02
34	10.0	118.88	4.78	15,0	155.15	5.04	0.77
Mean	13.7	195.00	5.19	13.5	208.90	5.27	0.96
SD	1.9	80.09	0.41	2.5	80.27	0.41	0.23
CA	13.8	41.07	7.83	18.3	38,43	7.73	24.25
Median	14.0	180.88	5.20	15.0	182.71	5.21	0.99
Geo Mean	13.5	180.09	5.18	13.3	193.65	5.25	0,93
Test/Ref R	atio						
Ratio of M	eans %		93.35				
	eo Means %		93.00				
-	ividual Ratios		0.96				
90% C.L			86%-99%				
Intra-CV			16.07%				

Fig. 10C

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CHRONOTHERAPEUTIC DILTLAZEM FORMULATIONS AND THE ADMINISTRATION THEREOF

This application is a continuation-in-part application of 5 U.S. patent application Ser. No. 09/465,338 filed Dec. 17, 1999 now abandoned claiming priority from Canadian Patent Application No. 2,292,247 filed Dec. 10, 1999. This application also claims priority from a Canadian Patent Application filed May 4, 2000.

FIELD OF INVENTION

This invention relates to once daily preparations comprising Diltiazem and pharmaceutically acceptable salts thereof, 15 such as the hydrochloride salt, suitable for evening administration to patients suffering hypertension and/or angina. This invention also relates to a method for evening administration of such once daily preparations to patients for the treatment of the patients' hypertension and/or angina.

BACKGROUND OF THE INVENTION

Diltiazem, a benzothiazepine, is an orally active calcium channel blocker (calcium-antagonist) with relatively high 25 selectivity for vascular smooth muscle that is effective in the treatment of hypertension and angina pectoris. Today, persons having these conditions take prescribed once daily preparations of Diltiazem generally to maintain constant levels of the drug in the body over a 24-hour period. Until 30 recently the timing of the taking of the medicine wasn't considered an important consideration by the medical community. Doctors generally did not take into account the natural circadian variation in the body's physiological functions. Researchers have now found that the timing of the 35 taking of a medicine can affect the way the human body responds to the medicine. The science of treating the human body taking into account the natural circadian variation is Chronotherapeutics. Chronotherapeutics relies on the praccorrect site of action at the most appropriate time period for the particular disease or condition. In man, blood pressure does not remain constant during day and night. Early in the morning blood pressure begins to rise from the low levels reached during sleep. Increases in blood pressure are accom- 45 panied by increases in heart rate caused by the chemicals generated by the body and delivered into the blood stream. Epidemiological studies have indicated that the greatest incidence of heart problems such as stroke, heart attack. myocardial ischemia and sudden cardiac death occur during 50 the early morning waking hours when the blood pressure is rising in response to the natural circadian rhythm. After normally rising in the morning, blood pressure remains elevated during the day until generally early evening when it starts to fall to its lowest level during sleep.

In one study, evening medication with Diltiazem for treatment of hypertension for effect the next morning has been stated to be more efficacious than other dosage schedules. Administration Time-Dependent Effects of Diltiazem on The 24-Hour Blood Pressure Profile of Essential Hyperten- 60 sion Patients, Isao Kohno et al. (Chronobiology International 14(1), 71-84, (1997.) In the report of the study, Herbesser RTM (200 mg) was identified as the Diltiazem preparation. Herbesser R™ is a Diltiazem formulation comprising a mixture of immediate release diltiazem-contain- 65 ing microspheres and sustained release diltiazem—containing coated microspheres. According to the report, following

a single dose (200 mg) administration, the time of peak plasma diltiazem concentration occurred at 12.5 hours after administration. The peak plasma diltiazem concentration Cmax in the persons studied was 107 mg/ml. Following multiple dosages of 200 mg Diltiazem given over 7 days, the time of peak plasma diltiazem concentration (Cmax) was at 10 hours after administration. Cmax was 154 mg/ml.

However a careful review of the report shows inconsistencies which cannot support the authors' conclusions. Par-10 ticularly at page 80, the best results shown in the graph are with respect to morning treatment with this formulation. Moreover at page 82, the authors themselves acknowledge the study cannot lead to reliable conclusions "because the number of patients was too small". Further, an immediate release portion of the dosage in the order of 15% is not desirable for evening administration. When the blood pressure is naturally at its lowest, not only is there no need for further reduction at that time, but such reduction can harm the patient. Particularly, if the blood pressure is reduced below a minimum the patient is put at a greater risk for cardiovascular accidents including stroke. Further, the 15% immediate release diltiazem is no longer available when needed.

In A comparative study of the steady-state pharmacokinetics of immediate-release and controlled-release diltiazem tablets, O. R. Leeuwenkamp et al., Eur. J. Clin. Pharmacol (1994) 46:243-247, controlled release properties and relative systemic availabilities of two dosages of the same controlled release diltiazem tablet formulation were studied by comparing them as steady state with those of an immediate release formulation. In the testing, the diltiazem plasma concentration increased slowly from about 6 hours after the evening dose of both CR tablets (Diltiazem CR 90 mg and Diltiazem CR 120 mg) resulting in relatively high plasma concentrations in the early morning hours. The clinicians concluded that twice-daily treatment with diltiazem CR tablets can replace thrice-daily treatment with a conventional diltiazem IR tablet. According to the clinicians The early morning rise of the diltiazem plasma concentratice of delivering the correct amount of medication to the 40 tion, which might lead to a lower incidence of ischemic events, may be an important clinical advantage of both CR tablets.

> On Apr. 22, 1998, Searle Canada announced that its Chronovera (R) (controlled onset extended-release verapamil) a high blood pressure medication was now available in Canada. Chronovera (R) was, according to Searle Canada, specifically designed to work with the body's natural circadian variations and was designed to be taken once-a-day just before bedtime. Chronovera provided 24-hour blood pressure control but was designed to deliver peak concentrations of verapamil in the morning when the blood pressure, heart rate and incidence of cardiovascular events were highest. According to Searle Canada, simply changing the time you take the drug your physician has prescribed will not provide the same safety and effectiveness that is designed specially for chronotherapy using verapamil. According to Searle Canada, its Chronovera (R) is unlike traditional medications including extended-release (XL) and sustained-release (SR) formulations which are usually prescribed in doses that maintain relatively constant levels of the drug in the body over a 24-hour period or attempt to maintain relatively constant levels of the drug in the body over a 24-hour period. According to Searle Canada, the prior formulations do not take into account the natural circadian variations in the body's physiological functions.

Sustained-release, once-daily diltiazem formulations have been taught which may be considered the traditional medication (according to Searle Canada). They appear not to give the benefits meant to be achieved by chronotherapy.

For example, in Pharmacokinetic Properties and Antihypertensive Efficacy of Once-Daily Diltiazem, J. G. Kelly et Journal Cardio-Vascular Pharmacology, 17:6:957-963, (1991), the controlled-release formulation of diltiazem released a proportion of the diltiazem relatively rapidly with the remainder released over a period extending to 24-hours. During in vitro dissolution testing 15% of the diltiazem in the dosage form was released in the first two hours, 54% was released in the first six hours, 89% in the first 13 hours and all of the remainder was released between 13 and 24 hours after administration. The diltiagem cansules contained either 120 mg or 240 mg of diltiazem. It should be 15 noted that no difference is shown between the placebo and dosages in the article at wake-up (between 5:00 a.m. and 8:00 a.m.).

U.S. Pat. No. 4,960,596 discloses slow release 12 hour diltiazem formulations whose dissolution, when measured in 20 accordance with United States Pharmacopoeia 21, purports to be within broad limits (between 5% and 35% after one hour, between 15% and 40% after two hours, between 20% and 50% after three hours, between 30% and 75% after four hours, between 40% and 80% after six hours and between 55% and 95% after eight hours). The examples in the patent, however, provide more specific range limitations specifying range limitations for the formulations exemplified such as at column 4, lines 8-10 and column 5, lines 60-62. In the first series of examples the release into aqueous medium was measured using the method of USP No. 21 of 10%-20% after one hour, 30%-35% after four hours and 60%-75% after eight hours. In the later examples, the release into aqueous medium was measured using the method of USP No. 21 at 15%-35% after one hour, 55%-75% after four hours, 75%-95% after eight hours. These formulations were, however, twice a day (b.i.d.) formulations.

A series of patents have issued to Elan Corporation p.l.c. involving controlled absorption diltiazem pellet formulations for oral administration in which each pellet has a core comprising diltiazem or a pharmaceutically acceptable salt thereof in association with a specified organic acid covered by an outer membrane which permits release of diltiazem from aqueous medium in accordance with U.S. Pharmacopoeia XX (Paddle Method) in buffered media at pH 1.5, pH 4.0 and pH 7.0. These are U.S. Pat. Nos. 4,721,619; 4,891, 230; 4,894,240; 4,917,899; 5,002,776; 5,219,621; 5,336, 504; 5,364,620 and 5,616,345.

In U.S. Pat. No. 4,721,619, dissolution rates of the pellets of examples are found at column 4, lines 41–49 and column 5, lines 5–12. The formulations, however are for 12 hour. The formulations of U.S. Pat. No. 4,891,230 are also for administration every 12 hours.

U.S. Pat. No. 4,894,240 purports to provide formulations for once-daily administration and specifies a general dissolution pattern at column 2, lines 43–52 and a more restricted dissolution pattern at column 3, lines 3–12. The dissolution rates are determined according to U.S. Pharmacopoeia XXI in 0.05M KCl at pH 7.0 and at 100 r.p.m. The examples of the patent, however, provide a more limited dissolution pattern under U.S. Pharmacopoeia XXI (Paddle Method) at column 7, lines 30–34 and 47–51, at column 8, lines 16–20, 32–36 and 49–53 and at column 8, lines 66—column 9, line 5. Similar examples are provided at columns 9, 10, 11 and 65 12. Nothing is taught with respect to formulations suitable as chronotherapeutics.

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U.S. Pat. Nos. 4,917,899, 5,364,620 and 5,616,345 are to the same effect. So are the remaining Elan patents. Nothing in these patents teach formulations suitable as chronotherapentics.

U.S. Pat. No. 5,529,790 purports to teach a delayed sustained-release pharmaceutical preparation in which a water-soluble drug core is surrounded by a hydratable diffusion barrier which delays drug release for about two to ten hours. While diltiazem hydrochloride dissolution patterns were provided in accordance with the U.S.P. basket dissolution method specified, no Cmax or the timing of the maximum blood levels is provided. The dissolution rates of the active are not appropriate for a suitable chronotherapeutic (see also U.S. Pat. Nos. 5,376,384 and 5,478,573).

U.S. Pat. Nos. 5,288,505 and 5,529,791 relate to extended-release galenical formulations of diltiazem or pharmaceutically acceptable salts thereof which comprise beads in which the active ingredient is in association with a wetting agent and which beads are coated by a microporous membrane. The Cmax of some formulations given in the patents provide for a Cmax after about 8-12 hours. Where the dosing of the formulations of the patents yields maximum diltiazem blood plasma levels (Cmax) of about 145 ng/ml, the Cmax is at about or less than 8 hours.

The applicants are also aware of a formulation marketed under the trade mark Tiazac™ a diltiazem HCl 24-hour sustained-release formulation based on teachings of U.S. Pat. Nos. 5,529,791 and 5,288,505.

Following chronic administration of Tiazac (240 mg once daily), the average peak plasma Diltiazem concentration (Cmax) is 183 ng/ml (multiple dosage) which occurred after about 7 hours past dose administration. TiazacTM provides a bioavailability of approximately 59% of the total Diltiazem in the first 12 hours and 41% in the second 12 hours (after 12 hours, 59%; after 16 hours 77% and after 20 hours 90%).

In an article entitled Effect of Morning Versus Evening Dosing of Diltiazem on Myocardial Ischemia Detected by Ambulatory Electrocardiographic Monitoring in Chronic Stable Angio Pectoris, PRA KASH, C. Deedwanian et al., The American Journal of Cardiology, Vol. 80, Aug. 15, 1997, p. 421-425, the authors compare a.m. and p.m. dosing without using an appropriate dosage form for p.m. The Tmax is achieved between 2-6 hours at steady state.

In an article The Influence of Time Administration on the Pharmacokinetics of a Once A Day Diltiazem Formulation: Morning Against Bedtime, Jean Thiffault et al., Biopharmaceutics & Drug Disposition, Vol. 17, 107-115 (1996), the once-a-day diltiazem formulation given at 2200 hours for seven days gave according to the article "significantly higher plasma concentrations of diltiazem in the early morning hours when the incidence of cardiovascular events is higher". The diltiazem dosages comprise 240 mg taken at 10:00 p.m. (22:00 hours) and maximum concentrations (Cmax) were achieved of 120 ng/ml after about six-eight hours of dosing. Unfortunately, the proposed system covers only the period from 2:00 a.m. to 8:00 a.m. To be a true chronotherapeutic, the time period covered should be between about 6:00 a.m. and noon. Moreover, this formulation when given at night leads to significantly lower bioavailability than if given in the morning.

It is therefore an object of this invention to provide diltiazem preparations suitable for once-a-day administration in the evening for providing effective dosage amounts in the blood of diltiazem in the moming when blood pressure begins to rise from the low levels reached during sleep, so as to be suitable as a chronotherapeutic preparation. Case 1:05-cv-00586-GMS

It is a further object of this invention to provide a method of administration of the diltiazem preparations suitable as a chronotherapeutic so as to be effective in the morning at a time when the patient has most need of the diltiazem preparation. Further and other objects of the invention will be realized by those skilled in the art from the following summary of the invention and detailed description of embodiments thereof.

SUMMARY OF THE INVENTION

According to one aspect of the invention, there is provided a controlled-release Galenical preparation (such as a tablet and a capsule) of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts 15 thereof, such as the hydrochloride salt, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg or more (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of 20 Diltiazem in the blood at between about 10 hours and about 15 hours (preferably about 11-about 13 hours) after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and the preparation is adapted to release the Diltiazem

- (i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII (at 100 rpm in 900 ml of water):
 - (a) between about 1% and about 15% after about 2 hours. preferably between about 4% and about 8% after 2 hours;
 - (b) between about 7% and about 35% after about 4 hours preferably between about 16% and about 21% after 4 35
 - (c) between about 30% and about 58% after about 8 hours preferably between about 44% and about 52% after 8 hours;
 - (d) between about 55% and about 80% after about 14 40 hours preferably between about 69% and about 76% after about 14 hours; and
 - (e) in excess of about 75% after about 24 hours and preferably more than about 85% after 30 hours.

and/or (ii) into a buffered medium (such as, for example, phosphate buffer (U.S.P.)) having a pH between about 5.5 and about 6.5, preferably about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium: 50

- (a) between about 1% and about 25% after about 2 hours, preferably between about 4% and about 15% after 2 hours:
- (b) between about 7% and about 45% after about 4 hours preferably between about 16% and about 30% after 4 55
- (c) between about 30% and about 68% after about 8 hours preferably between about 44% and about 62% after 8 hours:
- preferably more than 80% after 24 hours.

Preferably no initial retard or delay is built into the preparation retarding/delaying release of Diltiazem from the preparation. Preferably the release rate from the preparation of the Diltiazem is less than about 15% of the total active per hour during dissolution. The preparation may be a diffusion controlled preparation such as, for example, a preparation

incorporating the use of microgranules found, for example, in capsules and tablets; tablets; and coated tablets.

The preparation may comprise a plurality of microgranules or pellets, each microgranule comprising a central core or bead containing the form of diltiazem coated with a microporous membrane. The microgranules or pellets may be included in a capsule which dissolves when swallowed to release the microgranules or pellets. The preparation may also comprise a tablet in which the microgramules have been 10 compressed to form the tablet. When compressed into tablet form, wax placebo beads (as known by persons skilled in the art) are preferably included to absorb the shock placed on the microgranules (core and membrane) during the tableting process. By doing so, the integrity of the microgranules containing the Diltiazem active remains intact and the release rate from the preparation is not affected. The tablet may also be coated or uncoated. The preparation may also comprise a sustained-release tablet coating from which preparation the Diltiazem is released. In this regard, the sustained release coating may be applied (sprayed onto) to each tablet.

Where the preparation comprises microgramules or pellets (for example) in the capsule or tablet (made, for example, by compressing the microgranules (with preferably wax placebo beads)), the central core may comprise Diltiazem or a pharmaceutically acceptable salt thereof associated with a wetting agent. The Diltiazem may be mixed (in whole or in part) with the wetting agent or may not be mixed with the wetting agent. The wetting agent assists to maintain the solubility of the Diltiazem in each microgranule, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which each of the microgranules of the preparation will meet in the gastrointestinal tract.

If the Diltiazem and/or pharmaceutically acceptable salt is not mixed with the wetting agent then the microporous membrane should comprise with suitable adjuvants, a waterdispersible or water-soluble polymer (such as HPMC) and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer such as Eudragit NE30D (a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester) which hydrates the microgranule (including core). If the composition comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent, the 45 microporous membrane is preferably the same. However, it may also comprise any suitable membrane which gives to the preparation the required dissolution characteristics.

In this regard, the preferred microporous membrane comorises Eudragit NE30D and hydroxypropylmethylcellulose. This membrane will hydrate the core within the microporous membrane which, for example, may contain diltiazem surrounding a neutral pellet of sugar. The Eudragit NE30D in the membrane expands when it encounters gastrointestinal fluid to greater than 365% of its original size (elongation). This expandability of the membrane gives it the ability to hydrate the membrane and core. The mechanism of release is postulated to be that the membrane will swell while the fluids penetrate and hydrate the core and dissolve the diltiazem and wetting agent. This mechanism is, it is (d) in excess of about 75% after about 24 hours and 60 thought, driven by the concentration gradient through the membrane (high concentration inside and low concentration outside)

When Eudragit RS and Eudragit RL are combined to form the microporous membrane, the membrane can expand only very little before breakage or fracturing. The reason is that Eudragit RS expands minimally (about 6%) before the membrane material breaks or fractures changing its release

mechanism from the core. Thus, the mechanism of release from this membrane is thought to be by "washing" the diltiazem through pores created when a plasticizer incorporated in the membrane is released in the gastrointestinal fluid. The diltiazem at the outer surface of the core would be washed from the core through the pores of the microporous membrane, then the diltiazem next presenting itself to the fluids after "washing" of the uppermost (outermost) diltiazem, and so on.

Instead of the wetting agent, any other suitable dissolution 10 agent may be used to assist the release of the Diltiazem from the preparation. For example, instead of the preferred surface active (wetting) agent (surfactant), an organic acid (such as adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid and the like) may be 15 incorporated in the core. In this regard, the presence of the organic acid in the core permits the diltiazem in the core to dissolve when the composition passes into the higher pH regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble. One of the membranes 20 which may be used (though not preferred) is the combination of Eudragit RS and Eudragit RL disclosed in U.S. Pat. No. 4,721,619. (See column 1, lines 55-68 and column 2, lines 44-68.) The '619 patent also mentions the use of hydroxypropylmethylcellulose as a water-soluble mem- 25 brane. The mechanism of release in this case is not by hydration of the core but rather by "washing" the Diltiazem through the pores created in the membrane (for example when the plasticizer in the membrane is released in the gastrointestinal fluid).

The Diltiazem may be present in the core in, for example, the hydrochloride salt form, in which event no dissolution agent may be required in the core.

Suitable preparations such as capsules of the microgranules making up the total Diltiazem active present, may 35 comprise, in the core, Diltiazem hydrochloride between about 50% and about 85% (% w/w of the total preparation (for example, about 69% to about 73%)), a wetting agent (such as sucrose stearate) between about 2% and about 25% (% w/w of the total preparation) (for example about 7% to 40 about 8%) together with suitable adjuvants in the core, and in the membrane between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose (for example about 0.3% to about 0.6%), and between about 5% 45 and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (such as Eudragit NE30D) (for example about 7% to about 11%).

The microgranules may also be compressed into tablets so using suitable excipients. The percentages may be as described above. The tablets may be mamfactured, as discussed above, using the microgranules with wax placebo beads and compressing the combination into tablets in the presence of, for example, hydrogenated vegetable oil, 55 sodium starch glycolate and silicone dioxide which have been blended with the microgranules and wax placebo beads before tableting. The tablets may then be coated or uncoated.

According to another aspect of the invention, there is provided a controlled-release Galenical preparation (such as 60 a tablet and a capsule) of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, such as the hydrochloride salt, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg or more (as desired) of the form of Diltiazem 65 associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of

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Diltiazem in the blood at between about 10 hours and about 15 hours (preferably about 11-about 13 hours) after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with food (such as a standardized FDA breakfast) and without food according to the same FDA guidelines or criteria.

The FDA guidelines are those entitled:

"GUIDANCE ORAL EXTENDED (CONTROLLED) RELEASE DOSAGE FORMS IN VIVO BIOEQUIVALENCE AND IN VITRO DISSOLUTION TESTING" prepared under 21 CFR 10.90(b)(9) by Shrikant V. Dighe, Ph.D., Director, Division of Bioequivalence Office of Generic Drugs dated Sep. 3, 1993 and concurred by Roger L. Williams, M.D., Director, Office of Generic Drugs, Center for Drug Development Research dated Sep. 4, 1993 which is incorporated herein by reference; and

"GUIDANCE STATISTICAL PROCEDURES FOR BIOEQUIVALENCE STUDIES USING A STANDARD TWO-TREATMENT CROSSOVER DESIGN" prepared under 21 CFR 10.90(b)(9) by Mei-Ling Chem, Ph.D., Division of Bioequivalence Review Branch II dated Jun. 12, 1992 and Rabindra Patnaik, Ph.D., Division of Bioequivalence Review Branch II dated Jun. 26, 1992, approved by Shrikant V. Dighe, Ph.D., Director, Division of Bioequivalence dated Jun. 29, 1992 and concurred by Roger L. Williams, M.D., Director, Office of Generic Drugs dated Jun. 29, 1992 which is incorporated herein by reference.

In small part the said "GUIDANCE" documents provide as follows:

Pharmacokinetic Analysis of Data: Calculation of area under the plasma concentration-time curve to the last quantifinble concentration (ÅUC_{0-x}) and to infinity (AUC_{0-x}), C_{mex} and T_{mex} should be performed according to standard techniques.

Statistical Analysis of Pharmacokinetic Data: The log transformed AUC and C_{max} data should be analyzed statistically using analysis of variance. These two parameters for the test product should be shown to be within 80-125% of the reference product using the 90% confidence interval. See also Division of Bioequivalence Guidance Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design.

Statistical Analysis of Pharmacokinetic Data: The log transformed AUC and C_{max} data should be analyzed statistically using analysis of variance. These two parameters for the test product should be shown to be within 80–125% of the reference product using the 90% confidence interval. Fluctuation for the test product should be evaluated for comparability with that for the reference product. For further information on statistical analysis, see the Division of Bioequivalence Guidance Statistical procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design.

2. Multiple Dose Studies

At a minimum, the following pharmacokinetic parameters for the substance(s) of interest should be measured in a multiple dose bioequivalence study:

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- a. Area under the plasma/blood concentration—time curve from time zero to time τ over a dosing interval at steady state (AUC_{0-τ}), where τ is the dosing interval.
- b. Peak drug concentration (C_{max}) and the time to peak 5 drug concentration (T_{max}), obtained directly from the data without interpolation, after the last dose is administered.
- c. Drug concentrations at the end of each dosing interval during steady state (C_{min}) .
- d. Average drug concentration at steady state (C_{aν}), where C_{aν}-AUC_{0-ν}/τ.
- e. Degree of fluctuation (CF) at steady state, where DF=100%×(C_{max} - C_{min})/ C_{av}
- Evidence of attainment of steady state for the test and 15 reference products should be submitted in the bioequivalence study report.
- B. Statistical Analysis
 - Parametric (normal-theory) general linear model procedures are recommended for the analysis of pharmacokinetic data derived from in vivo bioequivalence studies. An analysis of variance (ANOVA) should be performed on the pharmacokinetic parameters AUC and C_{max} using General Linear Models (GLM) procedures of SAS (4) or an equivalent 25 program. Appropriate statistical models pertaining to the design of the bioequivalence study should be employed. For example, for a conventional two-treatment, two-period, two-sequence (2x2) randomized crossover study design, the statistical model often includes factors accounting for the following sources of variation:
 - 1. Sequence (sometimes called Group or Order)
 - 2. Subjects, nested in sequences
 - 3. Period (or Phase)
 - Treatment (sometimes called Drug or Formulation)
 The sequence effect should be tested using the [subject
 - The sequence effect should be tested using the [subject (sequence)]mean square from the ANOVA as an error term. All other main effects should be tested against the residual error (error mean square) from the ANOVA. The LSMEANS statement should be used to calculate least squares means for treatments. The ESTIMATE statement in SAS should be used to obtain estimates for the adjusted differences between treatment means and the standard error associated 45 with these differences.
 - The two one-sided hypotheses at the α =0.05 level of significance should be tested for AUC and C_{max} by constructing the 90% confidence interval for the ratio between the test and reference averages.
- III. Logarithmic Transformation of Pharmacokinetic Data A. Statistical Assumptions
 - The assumptions underlying the ANOVA are (5):
 - 1. Randomization of samples
 - 2. Homogeneity of variances
 - 3. Additivity (linearity) of the statistical model
 - 4. Independency and normality of residuals
 - In bioequivalence studies, these assumptions can be interpreted as follows:
 - The subjects chosen for the study should be randomly assigned to the sequences of the study.
 - The variances associated with the two treatments, as well as between the sequence groups, should be equal or at least comparable.
 - 3. The main effects of the statistical model, such as subject, sequence, period and treatment effect for

- a standard 2x2 crossover study, should be additive. There should be no interactions between these effects.
- The residuals of the model should be independently and normally distributed. In other words, data from bioequivalence studies should have a normal distribution.
- If these assumptions are not met, additional steps should be taken prior to the ANOVA including data transformation to improve the fit of the assumptions or use of a nonparametric statistical test in place of ANOVA. However, the normality and constant variance assumptions in the ANOVA model are known to be relatively robust, i.e., small or moderate departure from each (or both) of these assumptions will not have a significant effect on the final result.
- B. Rationale for Log Transformation
- 1. Clinical Rationale
 - In a meeting in September 1991, the Generic Drugs Advisory Committee (GDAC) concluded that the primary comparison of interest in a bioequivalence study was the ratio rather than the difference between average parameter data from the test and reference formulations. Using log transformation, the general linear statistical model employed in the analysis of bioequivalence data allows inferences about the difference between the two means on the log scale, which can then be retransformed into inferences about the ratio of the two averages (means or medians) on the original scale. Log transformation thus achieves the general comparison based on the ratio rather than the difference (6).
- 2. Pharmacokinetic Rationale
 - Westlake (7,8) observed that a multiplicative model is postulated for pharmacokinetic parameters in bioavailability/bioequivalence studies, i.e., AUC and C_{max} (but not T_{max}). Assuming that elimination of the drug is first order and only occurs from the central compartment, the following equation holds after an extravascular route of administration:

 $AUC_{0-\infty} = FD/CL$ = $FD/(VK_t)$

- where F is the fraction absorbed, D is the administered dose, and FD is the amount of drug absorbed. CL is the clearance of a given subject which is the product of the apparent volume of distribution (V) and the elimination rate constant (K).²
- $(K_e)^2$ Note that a more general equation can be written for any multi-compartmental model as AUC_{0-m} =FD/ $(V_{ab}V_{ab})$, where V_{ab} is the volume of distribution relating drug concentration in plasma or blood to the amount of drug in the body during the terminal exponential phase, and λ_i is the terminal slope of the concentration-time curve.
- The use of AUC as a measure of the amount of drug absorbed thus involves a multiplicative term (CL) which might be regarded as a function of the subject. For this reason, Westlake contends that the subject effect is not additive if the data is analyzed on the original scale of measurement.

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Logarithmic transformation of the AUC data will bring the CL (VK,) term into the equation in an additive fashion.

$1nAUC_{0-\infty}=1nF+1nD-1nV-1nK_3$

Similar arguments were given for Cmex. The following equation applies for a drug exhibiting one compartmental characteristics:

$C_{max} = (FD/V) \times e^{-Ke\Delta Tman}$

where again F, D and V are introduced into the model in a multiplicative manner. However, after logarithmic transformation, the equation becomes

1nCmax=1nF+1ND-1NV-KeTmax

Log transformation of the C_{max} data also results in the additive treatment of the V term.

3. Statistical Rationale

Logarithmic transformation of the data from bioequivalence studies can be used to circumvent 20 the use of estimates of the reference product average for computation of the confidence interval for the ratio of product averages. This is an advantage for the cases where a least squares estimate for the reference product mean is not well defined. Standard parametric methods are illsuited to making inferences about the ratio of two averages, though some valid methods do exist (9). Log transformation changes the problem to one of scale) of two averages, for which the standard methods are well suited.

Many biological data correspond more closely to a log-normal distribution than to a normal distribution. The plasma concentration data including the derived parameters AUC and Cmax tend to be skewed, and their variances tend to increase with the means. Log transformation is likely to remedy this situation and make the variances independent of the mean. In addition, frequency distributions skewed to the left (with a long tail to the right) are often made more symmetrical by log transforms-

This argument is actually less persuasive than the argument based on the additivity of the statistical model because it is based largely on the betweensubject distribution of AUC and Cmex values. For crossover studies, it is largely the within-subject distribution of values that determines the validity and efficiency of the standard parametric methods of analysis.

Despite the arguments regarding the effect of log transformation on normality of bioequivalence data, the division of Bioequivalence recognizes that the limited sample size (20-30 subjects) in a bioequivalence study precludes a reliable determination of the underlying normal distribution of the data set either with or without log transformation.

C. General Procedures

Based on the arguments in the preceding section, the Division of Bioequivalence recommends that the pharmacokinetic parameters AUC and Cmax be log transformed. Firms are not encouraged to test for 65 normality of data distribution after log transformation, nor should they employ normality of data

distribution as a justification for carrying out the statistical analysis on the original scale.

Robustness of a balanced study to nonnormality of the data plus use of log transformation will be adequate in most cases.

If a firm believes that the data of a particular bioequivalence study should be statistically analyzed on the original scale rather than the log scale, justification based upon a sound scientific rationale, as well as the statistical methods to be used, ought to be submitted to and reviewed by the Division of Bioequivalence.

Thus according to another aspect of the invention, the results of biostudies employing a formulation according to 15 an embodiment of the invention, clearly show that when given at different times (P.M. or A.M. dosing) and under different conditions (with and without food) though they achieve their maximum bioavailability at the same Tmax when the formulation is given at night (no food) a higher bioavailability (for example a significantly higher bioavailability exceeding 25% (C_{max}) is attained than when given in the morning without food (according to FDA guidelines) and bioequivalence when given with food or without food in the morning according to the FDA guidelines.

According to another aspect of the invention, a method of treatment of a patient's hypertension and/or angina is provided comprising administration of a preparation of Diltiazem described above, to the patient in the evening for example at about 7:00-about 11:00 p.m. for effective treatmaking inferences about the difference (on the log 30 ment of the patient's hypertension and/or angina the next morning, for example between about 6:00 a.m. and about

> According to another embodiment of the invention a method of treatment of a patient's hypertension and/or angina is provided comprising administration of a preparation which exhibits a higher bioavailability (exceeding, for example, 25%) when given at night compared to when given in the morning without food according to FDA guidelines or criteria and bioequivalence when given with food (for example given a standardized FDA breakfast) and without food according to the same FDA guidelines or criteria.

Thus a 24-hour diltiazem preparation is provided wherein the Cmmx of diltiazem in the blood is provided from about 10-15 hours after administration of a single dosage to a patient or about 9-15 hours after multiple dosages over a number of days and displays the dissolution pattern described above determined according to USP 23, page 1791 using Apparatus 1. Apparatus 1 is described as consisting of the following:

a covered vessel made of glass or other inert, transparent material1; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size that permits holding the temperature inside the vessel at 37 ±0.5° during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom. It is 160 to 175 mm high, its inside diameter is 98 to 106 mm, and its nominal capacity is 1000 mL. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.2 The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph, within +4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in FIG. 1. Unless otherwise specified in the individual monograph, use 40-mesh cloth. A basket having a gold coating 0.0001 inch (2.5 μ m) thick may be 10 used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is maintained at 25±2 mm during the test.

¹ The materials should not sorb, react, or interfere with the specimen being 15 tested.

² If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.

(taken from USP 23)

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According to another aspect of the invention, where the preparations comprise cores wherein the diltiazem is in association with a wetting agent, the wetting agent may be selected from:

sugars;

saccharose, mannitol, sorbitol;

lecithins:

 $\rm C_{12}$ to $\rm C_{20}$ fatty acid esters of saccarose, commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.) such as sucrose stearate marketed under the trade name of Crodesta;

xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene (Brijs, Renex and Eumulgines, Henkel, RFA);

sorbitan fatty acid esters (Span, Atlas, U.S.A.);

polyglycides-glycerides and polyglycides-alcohols esters (Gelucires, Gattefosse, France)

Metal salts such as NaCl or sodium lauryl sulphate

The microporous membrane may be of any suitable material or combination of materials known in the art. 40 of the invention. Where the wetting agent is in association with the diltiazem in the core and not mixed therewith, the microporous membrane should comprise a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer 45 such as a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester such as Eudragit NE30D. This enables the bead to be hydrated by the introduction of intestinal fluids into the bead hydrating the bead and therefore mixing the diltiazem and the wetting agent. The mem- 50 brane itself, because of the fluids passing through the membrane, will swell. This membrane acts differently from membranes which do not swell. These other non-hydratable or swellable membranes may be made-up, for example, of water-soluble or water-dispersible polymers or copolymers 55 and a water-, acid- and base-insoluble polymer such as Eudragit RS which swell less easily (owing to the reduced content in quaternary ammonium groups) and are only slightly permeable to active ingredients. This membrane is best suited for coating cores of Diltiazem mixed with a 60 wetting agent or organic acid.

Among materials which may be used to make the microporous membranes, may be mentioned particularly polyacrylates and polymethacrylates of the Budragit type, ethyl celluloses such as Ethocels from Dow U.S.A. and 65 Aquacoat of FMC U.S.A., hydroxypropylmethylcellulose, hydroxyethylcellulose and hydroxypropylcellulose.

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Additionally, adjuvants may be put in the formulation as required such as plastifying agents (plasticizer), pigments, fillers, lubricants and anti-foaming agents. For example talc and/or magnesium stearate may be used as a lubricant, dibutyl sebecate as plasticizer, titanium dioxide as a pigment, Tween 80 as an emulsifier and silicone oil as an anti-foaming agent.

The amount of the microporous membrane is adjusted to provide the sustained release characteristics described.

Thus embodiments of the invention have higher bioavailability (greater AUC and C_{max} at the same time (T)) when given at night than given in the morning without food according to the FDA guidelines discussed previously and are bioequivalent when given in the morning with food to formulation given in the morning without food according to the FDA guidance.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be illustrated with reference to the following examples and with reference to the following Figures:

FIG. 1: is a graph illustrating the Diltiazem Concentration (ng/mL) in the blood after a specified period after a single dose of a 300 mg Diltiazem capsule preparation made according to an embodiment of the invention.

FIG. 2: is a graph illustrating the Diltiazem Concentration (ng/mL) in the blood over a 24-hour period after giving multiple doses of the same 300 mg Diltiazem capsules referred to with respect to FIG. 1 but over a number of days,

FIG. 3: is a graph illustrating dissolution profiles generated according to USP 23 using Apparatus 1 (baskets) at 100 r.p.m. in 900 ml of water for capsule preparations made according to embodiments of the invention (120 mg, 180 mg, 240 mg and 300 mg of Diltiazem active).

FIG. 4: illustrates the dissolution profile of a 120 mg capsule preparation of Diltiazem HCI in water according to USP 23 (Apparatus 1-baskets) according to an embodiment of the invention.

FIG. 5: illustrates the dissolution profile of a 120 mg capsule preparation of Diltiazem HCl in gastric fluid according to USP 23 (Apparatus 1-baskets) according to an embodiment of the invention.

FIG. 6: illustrates the dissolution profile of a 120 mg capsule preparation of Diltiazem HCl in intestinal fluid according to USP 23 (Apparatus 1-baskets) according to an embodiment of the invention.

FIG. 7: is a graphic comparison of the blood level concentrations of a preparation (240 mg) made according to an embodiment of the invention and Dilacor (240 mg), a 24-hour oral sustained release dosage form of Diltiazem.

FIG. 8: is a graphic comparison of the blood level concentrations of a preparation (240 mg) made according to an embodiment of the invention and Tiazac (240 mg), a 24-hour oral sustained-release dosage form of Diltiazem.

FIG. 9: illustrates graphically the Mean Diltiazem Concentration when administration of the same dosage form, is given in the P.M., in the A.M. with food and in the A.M. with fasting (without food) by 29 persons.

FIG. 10: illustrates graphically the Mean Diltiazem Concentration when the dosage form is an open capsule sprinkled on applesauce and swallowed and the dosage form is swallowed intact by 30 persons.

Preparations were manufactured according to the percentages and constituents set out below: 10

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Comp	Component			
(1)	Diltiazem hydrochloride	69-73		
(2)	Microcrystalline cetholose (Avicet ph101)	8-9.5		
(3)	Povidone K30	12		
(4)	Sucrose stearate (crodesta F150)	7B		
(5)	Magnesium steamte NF	0.5-2.5		
(6)	Talc USP	0.5-5.0		
'n	Titanium dioxide (USP)	0.15-0.3		
(8)	Hydroxypropylmethylcellulose 2910	0.3-0.6		
(9)	Polysorbate 80 (tween)	0.010.025		
(10)	Simeticone C emulsion USP (dry of 30%)	0.010.015		
(11)	Eudragit NE30 D (dry of 30%)	7-11		
(12)	Purified water USP	0		

Two Examples of preparations given the above percentages were made as 120 mg and 180 mg strengths of Diltiazem (as the HCl salt) in capsule form.

Example 2

12		
(1)	120.00	
(2)	13.63-16.18	
(3)	1.7-3.41	
(4)	11.92-13.63	
(5)	0.852-4.26	
(6)	0.852-8.52	
(7)	0.256-0.511	
(8)	0.511-1.02	
(9)	0.01700.0426	
(10)	0.0170.0256	
(11)	11.92-18.74	
(12)	0	

Example 3

	Strength 80 mg capsule	Strength 180 mg capsule					
	180,00	(1)					
	20.44-24.27	(2)					
	2.56-5.11	(3)					
	17.88-20.44	(4)					
	1.278-6.38B	(5)					
	1.278-12.78	(6)					
	0.3830.767	(7)					
	0.7665-1.533	(B)					
	0.0256-0.0639	(9)					
	0.0255-0.383	(10)					
	17.886-28.106	(11)					
<u>:</u>	0	(12)					

240 mg, 300 mg, 360 mg and 420 mg strength preparations in capsule form of Diltiazem (as the HCl salt) were also prepared having the same percentages. They provide the release patterns shown in FIG. 3. The dissolution profiles of all of the strengths were generated from biobatches of capsules using Apparatus 1 (baskets) at 100 RPM in 900 ml of water in accordance with USP 23.

Less than 20% of the formulation is dissolved after about found the company of the property of the company of the company

Less than 20% of the formulation is dissolved after about four hours (for example between about 16%-21%) with less 65 than about 10% dissolved in the first two hours (for example between about 4%-about 8%). Less than about 50% is

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released after 8 hours (for example between about 44%-52%). Less than about 73% is released after 14 hours (for example 69%-76%). Preferably in excess of about 85% is released after 24 hours.

Specifically, samples of 120 mg capsules of Diltiazem HCI (made according to the embodiment of the invention) had the following dissolution profile:

		P	ercent	Disso	lved -	Time	Elapse	<u>d_</u>		
	2 h (%)		4 h (%)		8 h (%)		14 h (%)		24 h (%)	
	5	8	19	19	49	49	72	72	88	88
	4	5	16	14	32	44	76	69	93	85
	5	6	18	. 16	50	49	72	73	88	90
	7	6	21	17	54	48	76	72	92	87
	5	8	17	19	51	50	74	74	92	91
	6	7	81	19	52	52	74	75	90	92
Mean (%)	- 1	5	18		50		73	;	90)
RSD	2	1.3	10	.5	5	.1	2	2.7	- 7	2.6

Samples of 180 mg capsules of Diltiazem HCl (made according to an embodiment of the invention) had the following dissolution profiles:

		Percent Dissolved - Time Elapsed										
31	Lapsed Time	2 h (%)		4 h	4 h (%)		8 b (%)		ı (%)	24 h (%)		
٠,		8	7	21	20	52	52	76	73	91	89	
		6	7	19	20	52	51	76	73	93	90	
		5	6	16	18	48	50	72	72	89	90	
		6	7	19	18	52	49	76	72	98	88	
		7	7	20	19	51	51	73	74	91	91	
3:	5	8	7	20	21	51	51	74	73	92	91	
	Mean (%)	7	7	19		51		74	‡	91	l	
	RSD `	17	2.8	7	.4	2	.5	. :	2.1	1	1.7	

Samples of 240 mg capsules of Diltiazem HCl (made according to an embodiment of the invention) had the following dissolution profiles:

5		Percent Dissolved - Time Elapsed										
		2 h	2 h (%) 4 h (%)		8 b	8 b (%)		(%)	24 h (%)			
		6	4	19	16	46	48	73	71	86	86	
		6	5	18	15	48	45	70	68	85	84	
		5	5	18	17	49	49	71	72	86	88	
D		4	7	16	18	46	48	68	71	83	87	
		6	4	18	15	49	50	70	68	84	84	
		6	6	18	17	48	48	70	71	85	86	
	Mean (%)		5	17		48		70)	85	i	
	RSD	18	3.5	7	.7	2	.9	2	2.3		.7	

Samples of Diltiazem HCl capsules 300 mg (made according to an embodiment of the invention) had the following dissolution profile:

_	Percent	Disso	lved -	Time	Elapse	<u>d</u>		
2 h (%)		4 h (%)		8 h (%)		(%)	24 h (%)	
4	16	16	46	45	68	67	83	83
5	17	16	49	45	73	67	90	83
5	16	16	46	46	69	68	84	84
	_	h (%) 4 h 4 16 5 17	h (%) 4 h (%) 4 16 16 5 17 16	h (%) 4 h (%) 8 h 4 16 16 46 5 17 16 49	h (%) 4 h (%) 8 h (%) 4 16 16 46 45 5 17 16 49 45	h (%) 4 h (%) 8 h (%) 14 h 4 16 16 46 45 68 5 17 16 49 45 73	4 16 16 46 45 68 67 5 17 16 49 45 73 67	h (%) 4 h (%) 8 h (%) 14 h (%) 24 h 4 16 16 46 45 68 67 83 5 17 16 49 45 73 67 90

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•	•

Other Dissolution Profiles were determined of embodiments of the invention

-continued

Percent Dissolved - Time Elapsed

Medium-USP Water

Diltiazem 120 mg Capsules

1. /0/3	4 L /0/\	D 1. M/1	441.00	84 T Met	
					-

Apparatus:	USP #1	(baskets) at	100 rpm
------------	--------	--------------	---------

	(,					.,					
	5	5	16	16	46	46	69	69	83	87	•
	6	4	17	15	46	45	68	6B	82	86	10
	5	5	17	17	46	47	69	70	84	87	
Mcan (%)	:	5	16		46		69)	85	;	
RSD	13	3.2	3	.8	2	.4	7	2.3	:	2.8	
											. 15

Mean (%)		17 16	46 46		69 69	70 ?	84 85		
RSD	13	3.	2.4		2.3		2.8		
		 	 						. 15

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RSD RANGE

тіме (ы	2	4	8	14	24	
vessel 1	5%	19	49	72	BB	
vessel 2	4	16	52	76	93	
vessel 3	5	18	50	72	BB	
vessel 4	7	21	54	76	. 92	
vessel 5	5	17	51	74	92	
vessel 6	6	18	52	74 .	90	
vessel 7	8	19	49	72	88	
vessel B		14	44	69	86	
vessel 9		16	49	73	90	
vessel 10	6	17	48	72	87	
vessel 11	8	19	50	74	91	
vessel 12	7	19	52	75	92	
MEAN	6%	18	50	73	90	
m			-:-			

Additionally, the following Dissolution Profiles were obtained for the samples of 120 mg Diltiazem HCl Capsules:

Medium: Water

Diltiazem HCl Capsules

90

Hour 2

14

24

% Dissolved	Range		
(Average of 12 capsules)	[%]	RSD	
6	4-8	17.6	_
18	14-21	9.8	
50	44-54	5.1	
73	69-76	2.8	

86-93

2.5

35

Medium-Gastric

Apparatus: USP #1 (baskets) at 100 rpm

	Medium: Gastric Fl	uid		
	Diltiazem HCl Capsules % Dissolved	Range		
Honr	(Average of 12 capsules)	[%]	RSD	
2	5	36	18.8 .	<u> </u>
4	16	14-18	9.0	
8	49	47-52	3.5	
14	73 .	71–75	1.8	
24	87	8589	1.5	

TIME [b]	2	4	8	14	24
vessel 1	3	14	51	74	BB
vessel 2	6	17	48	72	85
vessel 3	5	17	49	72	85
vessel 4	5	15	48	72	87
vessel 5	4		47	71	86
vesse) 6	6	18	50	72	86
vessel 7		15	49	73	88
vessel 8	4	14	48	71	86
vessel 9	5	17	51	74	88
01 leazov	6	18	52	74	RB
vessel II	6	18		75	89
vessel 12	5	17	50	73	87
MEAN	5	16	49	73	87
SD	0.9	1.5	1.7	1.3	1.3
RSD	19.0	9.0	3.5	1.B	1.5
RANGE	3-6	1418	47-52	71-75	85-89

Medium-Intestinal

Apparatus: USP #1 (baskets) at 100 rpm

	Medium: Intestinal F	hid	
Hour	Diltiazem HCl Capsules % Dissolved (Avenge of 12 capsules)	Range [%]	RSD
2	5	3–7	26.0
4	17	1420	12.0
8	43	40-47	6.3
14	64	5369	8.1
24	78	65-85	B.1

		Dilti	szem 120 n	g Capsules	_	
io _	TIME (b)	2	4	8	14	24
	vessel 1	7	19	45	67	81
	vessel 2	4	14	40	64	79
	vessel 3	7	20	47	69	83
	vessel 4	5	19	46	68	83
	vessel 5		17	41	58	69
5	vessel 6		17	45	69	83
	vessel 7	4	17	40	53	65

-cor	шш	160

	Diltiazem 120 mg Capsules				
TIME [h]	2	4	8	14	24
vessel 8	5	17	42	65	78
vessel 9	5			58	73
vessel 10	5	17	47	68	85
vessel 11	4	15	44	64	81
vessel 12	4	15	43	64	B1
MEAN	5	17	43	64	78
SD	1.2	2.0	2.7	5,2	6.4
RSD	25.9	13.0	6.1	8.1	8.1
RANGE	3–7	14-20	40-47	53-69	65-8

Briefly, the dosages in Examples 1 (120 mg) and 2 (180 mg), the 240 mg, 300 mg, 360 mg and 420 mg dosages were manufactured by mixing the core (bead) ingredients (dilliazem, microcrystalline cellulose, povidone, sucrose stearate) by introducing the components into a planetary mixer and granulating same and mixing with purified water. The plastic mass was then extruded to provide an extrudate. The extrudate was subsequently spheronized to produce dilliazem spheres in admixture with the wetting agent. The spheres (cores) were dried in an oven and sieved to the appropriate size cores or beads.

The membrane was prepared by mixing the hydroxypropylmethylcellulose, titanium dioxide, talc, magnesium stearate, Polysorbate 80 and Simethacone C emulsion and thereafter combined with the Eudragit NE30D and water. The spheronized cores were coated with the appropriate thickness of membrane by spraying the cores, coating same. Thus the cores (beads) were coated with the coating suspension to produce the microgramules or pellets. The microgramules or pellets were then dried.

In more detail the process combines Diltiazem Hydrochloride USP, Microcrystalline cellulose NF (Avicel PH 101), Povidone K30 USP and Sucrose Stearate (Crodesta F160) as follows:

The following were screened through a 1.9 mm screen 40 and added to a mixer bowl:

Diltiazem

Avicel PH 101

Povidone K30.

To remove large agglomerates, the Crodesta 7.98 kg was 45 screened through a 1.0-1.2 mm screen and added to the same mixing bowl. The items were then blended in an AMF blender at 50 RPM. 1 kg of the above dry blend was set aside to be used as dusting powder (Diltiazem Dusting Powder). The remainder of the blend was continued to be blended at 50 rpm until adequately granulated. The granulated material was then loaded into the hopper of an extruder (such as EXDCS100 or EXDS 60). The granulation was extruded and without breaking up the extrudate, the extrudate was collected. The extrudate was then spheronized into the cores 55 (beads) of the desired size and were dusted as desired by the Diltiazem Dusting Powder set aside. The beads were then dried by spreading them on trays and drying in an oven set at about 57° C. The Drying Temp. was in the order of 55-60° C. for about 12 hours (in the order of 12-16 hours). The 60 dried cores (beads) were sieved to collect those of appropriate size (0.7-1.4 mm).

A Eudragit NE30D and hydroxypropylmethylcellulose coating suspension, was made. The following:

Magnesium Stearate NF

Tale USP

Titanium Dioxide USP

Hydroxypropylmethylcellulose 2910 USP (Pharmacoat 606)

Polysorbate 80 NF (Tween 80)

Simethicone C Emulsion USP

and pure water were combined within a Silverson Mixer. Water was first mixed with Polysorbate 80 and the Simethicone. The HPMC was then added, then titanium dioxide, then talc and then the Magnesium Stearate. The mixture was stored for 2 hours. The Budragit NE30D was screened through a 0.310 mm sieve and added to the mixture.

The beads were then coated with the suspension by using an AerocoaterTM and spraying the beads (which have been preheated to 26° C.) with the coating suspension to achieve the desired thickness (about 0.05 mm). The beads were then dried by spreading on trays and drying at 40-45° C. for 10-12 hours.

Diltiazem HCl 300 mg capsules made according to an embodiment of the invention were tested in a single dose study to determine their bioavailability, their Cmax and Tmax, their rate and extent of absorption. Blood sampling for drug content analysis was carried out at 0.0 (predrug) 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 24, 30, 36, 42 and 48 hours post-drug. Vital sign and 12—Lead ECG monitoring were conducted at 0 (predrug) 2, 6, 8 and 12 hours post-drug. The following was determined from the plasma study:

Mean Pharmacokinctic Parameters for Plasma Diltiazem (n = 41)

Parameter	1 x 300 mg Meun (% CV)
AUC (0-t)(ng.hr/mL)	2703.83 (36.26)
AUG (0-inf.)(ng.hr/mL)	2786,95 (36,39)
C _{max} (ng/mL)	146.33 (38.43)
T _{max} (hours)	13.17 (14.79)
t _{1/2} (hours)	6.96 (17.56)
Kol (hour-1)	0.102 (15.983)

(n ==	41)	
SAMPLE TIME (HOURS)	1 × 300 mg	
 0.00	0.00 ± 0.00	
1.00	0.76 ± 2.20	
2.00	4.92 ± 3.87	
3.00	10.97 ± 5.92	
4.00	20.01 ± 10.77	
5.00	33,46 ± 18.39	
6.00	70.21 ± 37.03	
8.00	95.43 ± 41.50	
10.00	110,16 ± 47,43	
12.00	132.84 ± 52.04	
14.00	139.54 ± 55.11	
16.00	126.35 ± 50.23	
18.00	105.74 ± 40.86	
24.00	62.84 ± 24.20	
	12.00 15.01	

42.00

25.67 ± 11.46

 7.50 ± 4.46

 13.40 ± 7.37

Mean Plasma Diltiazem Concentrations (ng/mL)

Mean Phamacokinetic Parameters for Piasma Diltiazem (n = 36)			
Parameter	Geometric Mean Arithmetic Mean (C.V.) 1 × 300 mg		
AUC (0-t bours)(ng.hr/mL)	2682.87		
	2872.06 (38.44)		
AUC (0-x)(ng.hr/mL)	1955,92		
	2075.00 (35.63)		
AUC (0-infinity)(ng.hr/mL)	2847.57		
	3055.19 (39.05)		
C _{max} (ng/mL)	134.96		
	144.00 (37.17)		
T _{max} (hours)**	13.00 (2.92)		
1 _{1/2} (hours)*	8.69 (22.K5)		
K _{*1} (hour ⁻¹)*	0.084 (22.860)		

These are arithmetic means (CV %).

With reference to FIGS. 1 and 2, it is clear the 300 mg capsule preparation made according to an embodiment of the invention provides the appropriate Diltiazem blood levels at the appropriate time to be suitable for administration as a chronotherapeutic-being given in the evening to 25 provide effective concentrations of Diltiazem the following morning. This suitability is illustrated with reference to FIGS. 7 and 8. In FIG. 7, the 240 mg Diltiazem preparation made according to the embodiment of the invention provides elevated blood levels that are effective all morning for 30 effective treatment of the patient with Diltiazem. However, the Dilacor formulation (given either in the evening or the following morning) does not protect the patient from 6:00 a.m.-noon, the more dangerous period.

The same is true with FIG. 8. Tiazac given in the morning, does not provide the protection. Further, peak plasma concentrations for Tiazac are achieved after about 7 hours after dose administration.

A 3-way single-dose study was undertaken using the same formulation (420 mg capsule) administered in the P.M. (10:00 P.M.) without food, and in the A.M. dosing with and without food.

3-Way Single-Dose Study

A: Formulation According to Embodiment of Invention 45 Fasting (AM Dosing)

B: Formulation According to Embodiment of Invention-Fed (AM Dosing)

C: Formulation According to Embodiment of Invention-(PM Dosing)

N=29

The results illustrated in FIG. 9A and FIG. 9B were found whose mean were graphically illustrated in FIG. 9.

A 2-way single-dose fasting study was undertaken using 55 the same formulation (420 mg capsule) administered in the following manners—capsule intact and capsule opened and sprinkled on applesance and ingested.

2-Way Single Dose Fasting Study

A: Formulation According to Embodiment of Inventions-Open Capsule Sprinkled on Applesance

B: Formulation According to Embodiment of Inventions-Capsule Intact

N=30 (FINAL DATA)

The results illustrated in FIGS. 10A, 10B and 10C were found whose mean were graphically illustrated in FIG. 10.

The preparations according to embodiments may also be made as tablets. The tablets may be made as compressed tablets in the desired strengths (for example 120 mg-540 mg or more Diltiazem) incorporating the microgranules. The tablets may even be scored to permit division into smaller

Tablets may be made as follows using the microgranules or pellets, wax placebo beads and hydrogenated vegetable oil, sodium starch glycolate and silicone dioxide as follows:

The microgranules of Diltiazem may be the following:

Magnesium Stearate

Titanium Dioxide

Hydroxypropylmethyl-Cellulose 2910

Polysorbate 80 Simethicone Emulsion

Eudragit NE30D Diltiazem Hydrochloride

Microcrystalline Cellulose

Povidone K30

Sucrose Stearate

Purified Water

The wax placebo beads may be the following:

Microcrystalline Wax NF Pregelatinized Starch

Sodium Starch Glycolate

Titanium Dioxide

Carbon Dioxide

The microgranules, wax placebo beads, hydrogenated vegetable oil, sodium starch glycolate and silicone dioxide may be combined and compressed into the desired strengths of tablets, for example 240 mg, 300 mg and 360 mg tablets. Briefly, to form the microgranules, Diltiazem HCl, Microcrystalline Cellulose, Povidone 30, Sucrose Stearate may be mixed to form a "dry blend". A 1 kg portion of the dry blend may be removed and stored in a separate labeled container as the Dusting Powder, for use in subsequent manufacturing steps (if desired). Following the removal of the Dusting Powder, Purified Water is added to the dry blend and mixed to create a plastic mass. The plastic mass is extruded through a 1.0 mm screen to form a spaghetti like extrudate. This extrudate is then spheronized into beads. During the spheronization process Dusting Powder is added to dry the beads and provide them with a smooth aspect (if required). The addition of Dusting Powder also prevents the newly spheronized beads from sticking together. The spheronized beads are tray dried for 12-16 hours and sieved to select beads that are larger than 0.7 mm and smaller than 1.4 mm in diameter.

The beads are loaded into a preheated (40-45° C.) fluid bed Aerocoater. Coating suspension is applied at an amount of 10% by spray coating. The resulting Diltiazem Microgranules (coated beads) are dried for between 10-12 hours and the dried coated beads are sieved to select coated beads that are larger than 0.7 mm and smaller than 1.7 mm in diameter.

For the manufacture of the placebo wax beads, Microcrystalline Wax, Pregelatinized Maize Starch, Sodium Starch Glycolate and Titanium Dioxide are mixed in a high shear mixer and heated to 64° C. (jacket temperature 70° C.). The resulting melt is cooled by the addition of liquid CO, to form the solid starters of the pellets. The pellet starters are mixed and the size is increased by the gradual turning of the impeller for a fixed timeperiod (mixing time is directly related to the impeller speed and the time to reach a temperature of 57±2° C.). The resulting beads are sieved to select beads larger than 0.7 mm and smaller than 1.4 mm in

^{**}This is median (±S.D.).

For manufacturing the Diltiazem chronotherapeutic tablets, the placebo wax beads and the microgranules of Diltiazem are blended at a ratio of about 2:3 (placebo wax beads: microgranules of Diltiazem) with Hydrogenated Vegetable Oil (lubricant), Sodium Starch Glycolate (disintegrant) and 5 Silicone Dioxide (lubricant) added. The blend is tableted under low pressure (approximately 6–8 Sc) to form the compressed Diltiazem Tablets.

In the compressed tablets, the placebo wax beads serve to absorb the shock placed on the microgranules of Diltiazem 10 during the tableting process. By doing so the integrity of the microgranules remains in tact and the release rate of the diltiazem is not affected.

As many changes can be made to the embodiments of the invention without departing from the scope thereof, it is intended that all material contained herein be determined as illustrative of the invention and not in a limiting sense.

The invention claimed is:

- 1. An orally administrable controlled-release composition comprising a pharmaceutically acceptable form of diltiazem selected from the group consisting of diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours, the dosage comprising at least one bead comprising a core and at least one coating, the at least one bead being formulated in an oral dosage form containing from about 120 mg to about 540 mg of the form of diltiazem, the diltiazem in the core of each bead associated with excipients, the at least one coating covering the core comprising an amount of a water swellable and diffusible coating which permits hydration of the core by gastrointestinal fluids, the water swellable and diffusible comprising the following constituents:
 - (i) an amount of at least one hydrophilic polymer which is selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, and hydroxypropylcellulose, and/or an amount of at least one lubricant which is selected from the group consisting of talc, and magnesium stearate; and
 - (ii) an amount at least one water-, acid- or base-insoluble neutral acrylic polymer, wherein said constituents (i) and (ii) which comprise said coating, the ratios thereof, and the amount of said coating are formulated such that said orally administrable composition:
 - A) in vitro exhibits the following in vitro release 45 characteristics;
 - (i) releases the diltiazem or a pharmaceutically acceptable salt thereof into an aqueous medium at the following rates when measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
 - (a) between about 1% and about 15% after about 2 hours:
 - (b) between about 7% and about 35% after about 4 hours;
 - (c) between about 30% and about 58% after about 8
 - (d) between about 55% and about 80% after about 14 hours;
 - (e) in excess of about 75% after about 24 hours; 60 and/or
 - (ii) releases the diltiazem or pharmaceutically acceptable salt thereof into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States 65 Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:

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- (a) between about 1% and about 25% after about 2 hours;
- (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;
- (d) in excess of about 75% after about 24 hours; and further wherein said orally administrable composition having said in vitro release characteristics results in a composition that:
- B) when orally given to humans exhibit the following properties:
- (i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
- (ii) bioequivalence when given in the morning with or without food according to the same FDA guidelines or criteria; and
- (iii) provides a Cmax of diltiazem in the blood at between about 10 hours and 15 hours after administration.
- 2. The controlled release preparation of claim 1 wherein said neutral acrylic polymer is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester.
- 3. The controlled-release preparation of claim 1 in which the form of diltiazem is adapted to be control released after administration of the preparation over a period of time and is more preferably adapted to release the diltiazem
- (i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
 - (a) between about 4% and about 8% after about 2
 - (b) between about 16% and about 21% after about 4 hours;
 - (c) between about 44% and about 52% after about 8
 - (d) between about 69% and about 76% after about 14 hours; and
- (e) and in excess of about 85% after about 24 hours; and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:
 - (a) between about 4% and about 15% after about 2 hours;
 - (b) between about 16% and about 30% after about 4 hours;
- (c) between about 44% and about 62% after about 8 hours:
- (d) in excess of about 80% after about 24 hours.
- 4. The preparation of claim 1 wherein the Cmax of diltiazem in the blood is obtained between about 11-about 13 hours after administration of the preparation.
- 5. The preparation of claim 1, 2, 3 or 4 wherein the form of diltiazem is Diltiazem HCl.
- The preparation of claim 4 wherein the preparation is a diffusion controlled preparation.
- 7. The preparation of claim 3 wherein the preparation releases the diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.
 - 8. The preparation of claim 7 in capsule form.
- 9. The preparation of claim 7 in tablet form.
- 10. The preparation of claim 7 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core

comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

- 11. The preparation of claim 10 wherein the diltiazem is mixed (in whole or in part) with the wetting agent.
- 12. The preparation of claim 11 wherein the wetting agent assists to maintain the solubility of the diltiazem in each microgramule, ensuring that the solubility of the diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.
- 13. The preparation of claim 12 wherein the membrane 10 comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.
- 14. The preparation of claim 10 wherein the preparation 15 comprises a mixture of the diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic 20 acid methyl ester which hydrates the preparation.
- 15. The preparation of claim 14 wherein the membrane comprises a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.
- 16. The preparation of claim 15 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgrammle, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).
- 17. The preparation of claim 11 wherein the diltiazem is mixed with the wetting agent and the membrane comprises an acrylic membrane and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.
- 18. The preparation of claim 7 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the diltiazem from the preparation.
- 19. The preparation of claim 18 wherein the dissolution agent is an organic acid comprising adipic acid, ascorbic soid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid which permits the diltiazem to dissolve in gastrointestinal fluids even when the microgramules pass into the regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.
- 20. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 1 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning, the method comprising administering to a patient in need thereof the preparation in the evening.

 33. A method of treatment of and/or angina comprising and and/or angina the next morning.
- 21. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 2 to the patient in the evening for 65 effective treatment of the patient's hypertension and/or angina the next morning.

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- 22. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 3 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 23. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 4 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 24. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 5 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 25. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 6 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 26. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 7 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
 - 27. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 8 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
 - 28. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 9 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
 - 29. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 10 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
 - 30. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 11 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
 - 31. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 12 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 32. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 13 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
 - 33. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 14 to the patient in the evening for effective treatment of the patient's hypertension and/or anging the next morning.
 - 34. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 15 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
 - 35. A method of treatment of a patient's hypertension and/or angina comprising the administration of the prepa-

- 36. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 17 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 37. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltinzem of claim 18 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 38. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 19 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 39. The preparation of claim 1 wherein the preparation contains 120 mg of diltiazem.
- 40. The preparation of claim 1 wherein the preparation contains 180 mg of diltiazem.
- The preparation of claim 1 wherein the preparation contains 240 mg of diltiazem.
- 42. The preparation of claim 1 wherein the preparation contains 300 mg of diltiazem.
- 43. The preparation of claim 1 wherein the preparation contains 360 mg of diltiazem.
- 44. The preparation of claim 1 wherein the preparation contains 420 mg of diltiazem.
- 45. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 39, 40, 41, 42, 43 or 44 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 46. The preparation of claim 15 wherein the wetting agent is selected from:

sugars;

saccharose, mannitol, sorbitol;

lecithins;

C12 to C20 fatty acid esters of saccarose;

xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene;

sorbitan fatty acid ester;

polyglycides-glycerides and polyglycides-alcohols ester, and metal salts.

- 47. The preparation of claim 10 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer selected from the group consisting of hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which enables the bead to be hydrated by the introduction of gastrointestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.
- 48. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 46 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 49. A method of treatment of a patient's hypertension and/or angina comprising the administration of the prepa-

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ration of diltiazem of claim 47 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

50. A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to claim 1 which comprises the following constituents:

0			% W/W
	(i) i	n the core:	
	(n)	Diltiszem hydrochloride	69-73
	(b)	Microcrystalline cellulose	8-9.5
_	(c)	(Polyvinyl Pyrrolidone)	1-2
5	(d)	Sucrose stearate	7B
	(ii) in the membrane:		
	(c)	Magnesium stearate NF	0.5-2.5
	(f)	Talc USP	0.5-5.0
	(g)	Titanium dioxide. (USP)	0.15-0.3
0	(<u>H</u>)	Hydroxypropylmethylcellulose 2910	0.3-0.6
	(i)	(Polyoxyethylene Sorbitan Monopleale)	0.01-0.025
	Ġ)	Simethicone C emulsion USP. (dry of 30%)	0.010.015
	(k)	a neutral acrylic polymer of acrylic acid	711
		ethyl ester and acrylic acid methyl ester	
		(dry of 30%)	
5		Purified water USP	0 (used for mixing).

- 51. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 50 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 52. The preparation of claim 10 in which the core and membrane comprise:
 - (i) in the core,
 - (a) between about 50% and about 85% (% w/w of the lotal preparation) of diltiazem or pharmaceutically acceptable salt thereof; and
 - (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

- (ii) in the membrane,
 - (c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of tale, and magnesium stearate;
 - (d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethyl-cellulose, hydroxypropylcellulose, and any combination thereof; and
 - (e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.
- 53. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 52 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 54. The preparation of claim 10 in which the core and membrane comprise:
 - (i) in the core,
 - (a) between about 69% and about 73% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

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(b) between about 7% and about 8% wetting agent (% w/w of the total preparation); together with suitable adjuvants; and

(ii) in the membrane,

- (c) between about 0.1% and about 50% of the total 5 preparation of lubricant selected from the group consisting of tale, and magnesium stearate;
- (d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of 10 hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and any combination thereof; and
- (e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid 15 ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.
- 55. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 54 to the patient in the evening 20 for effective treatment of the patient's hypertension and/or angina the next morning.
- 56. The preparation of claim 10 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads 25 serve to absorb the shock placed on the microgranules of diltiazem during the tablet process, together with suitable excipients and adjuvants.
- 57. A method of treatment of a patient's hypertension and/or angina comprising the administration of the prepa- 30 ration of diltiazem of claim 56 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 58. The controlled-release preparation of claim 2 in which the diltiazem is adapted to be control released after admin- 3 istration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically 4 acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:
 - (i) in the core,
 - (a) between about 50% and about 85% (% w/w of the total preparation) of diltiazem or pharmaceutically 4 acceptable salt thereof; and
 - (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

- (ii) in the membrane,
 - (c) between 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of tale, and magnesium stearate;
 - (d) between about 0.1% and about 2% of the total ible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and any combination thereof: and
 - (e) between about 5% and about 20% (% w/w of the 60 preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.
- 59. The preparation of claim 58 wherein the microgranules are in capsule form.
- 60. The preparation of claim 58 wherein the microgranules are in tablet form.

- 61. The preparation of claim 58 wherein the core and membrane comprise:
 - (i) in the core,
 - (a) between about 69% and about 73% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and
 - (b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

- (ii) in the membrane,
- (c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of tale, and magnesium stearate:
- (d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and any combination thereof; and
- (e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.
- 62. A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to claim 1, which preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

		% W/W
(i) i	n the core:	
(a)	Diltinzem hydrochloride	69-73
(b)	Microcrystalline cellulose	8-9.5
(c)	(Polyvinyl Pyrrolidone)	12
(d)	Sucrose stearate	7-8
(ii)	in the membrane:	
(c)	Magnesium steamte NF	0.5-2.5
(f)	Talc USP	0.5-5.0
(g)	Titanium dioxide. (USP)	0.15-0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3-0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01-0.025
(i)	Simethicone C emulsion USP. (dry of 30%)	0.01-0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	711
	Purified water USP	0 (used for mixing).

- 63. The preparation of claim 58 wherein the preparation is a tablet and the tablet comprises microgranules in assopreparation of water-soluble and/or water-dispers- 55 ciation with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of diltiazem during the tablet process, together with suitable excipients and adjuvants.
 - 64. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 58 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
 - 65. A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to claim 1, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form

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of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the wetting agent is selected from:

saccharose, mannitol, sorbitol;

lecithins:

C12 to C20 fatty acid esters of saccarose;

xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene;

sorbitan fatty acid esters;

polyglycides-glycerides and polyglycides-alcohols ester; and metal salts.

66. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 65 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

67. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of the pre ration of diltiazem of claim 63 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

68. A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to claim 1

wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a 30 microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

	% W/W	
(i) in the core:		
(a) Diltiazem hydrochloride	6973	4
(b) Microcrystalline cellulose	8-95	
(c) (Polyvinyl Pyrrolidone)	1-2	
(d) Sucrose stearate	78	
(ii) in the membrane:		
(c) Magnesium stearate NF	0.5-2.5	4
(f) Tale USP	0.5-5.0	
(g) Titanium dioxide. (USP)	0.15-0.3	
(h) Hydroxypropylmethylcellulose 2910	0.30.6	
(i) (Polyoxyethylene Sorbitan Monooleate)	0.01-0.025	
(i) Simethicone C emulsion USP. (dry of 30%)	0.01-0.015	
(E) neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester	7–11	5
(dry of 30%)		
Purified water USP	0 (used for mixing).	

69. A method of treatment of a patient's hypertension 55 and/or angina comprising the administration of the preparation of diltiazem of claim 66 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

70. A controlled-release preparation of pharmaceutically 60 acceptable form of diltiazem according to claim 3, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically 65 acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of tale, and magnesium stearate;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and any combination thereof; and

(e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of

the core by gestrointestinal fluids.
71. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 70 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

72. A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to claim 3, wherein the preparation comprises a plurality of microgramules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in 35 which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, and magnesium stearate;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and any combination thereof; and

(e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.

73. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 72 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

74. A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to claim 1 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the

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central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

- (i) in the core.
 - (a) between about 50% and about 85% (% w/w of the 5 total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and
 - (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

- (ii) in the membrane,
 - (c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of tale, and magnesium stearate;
 - (d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and any combination 20 thereof; and
 - (e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.
- 75. The preparation of claim 74 wherein the microgranules are in capsule form,
- 76. The preparation of claim 74 wherein the microgran- 30 ules are in tablet form.
- 77. The preparation of claim 74, 75 or 76 wherein the core and membrane comprise:
 - (i) in the core,
 - (a) between about 69% and about 73% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and
 - (b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

- (ii) in the membrane,
 - (c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of tale, and magnesium stearate;
 - (d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethyl-cellulose, hydroxypropylcellulose, and any combination thereof; and
 - (e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together 55 with suitable adjuvants.
- 78. The preparation of claim 74, 75 or 76 wherein the core and membrane comprise:

		% W/W
(i)	in the core:	
(a)	Diltiszem hydrochloride	69–73
(b)	Microcrystalline cellulose	8-9.5
(c)	(Polyvinyl Pyrrolidone)	1-2
(d)	Sucrose stearate	7-8
<u>(ii)</u>	in the membrane:	
(c)	Magnesium stearate NF	0.5-2.5
(1)	Tale USP	0.5-5,0
(g)	Titanium dioxide. (USP)	0.15~0.3
(p)	Hydroxypropylmethylcellulose 2910	0.3-0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01-0.025
(i)	Simethicone C comulsion USP. (dry of 30%)	0.01-0.015
(k)	a neutral acrylic	7–11
	polymer of acrylic acid ethyl ester and	
	acrylic soid methyl ester. (dry of 30%)	
	Purified water USP	0 (used for mixing).

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- 79. The preparation of claim 74 or 76 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax 25 placebo beads serve to absorb the shock placed on the microgranules of diltiazem during the tablet process, together with suitable excipients and adjuvants.
 - 80. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 74, 75 or 76 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 81. The controlled release preparation of claim 1 wherein said neutral acrylic polymer is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester.
- 82. The preparation of claim 70, 72 and 74 wherein the lubricant is selected from the group consisting of tale, and 40 magnesium stearate.
 - 83. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 81 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
 - 84. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltizzem of claim 82 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
 - 85. The preparation of claim 1 in capsule form.
 - 86. The preparation of claim 1 in tablet form.
 - 87. The preparation of claim 2 in capsule form.
 - 88. The preparation of claim 2 in tablet form.